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(54) Title: PEPTIDE ANALOGS OF THE ACTIVATED PLATELET BINDING SITE ON FACTOR XI

(57) Abstract

Synthetic peptide analogs of human factor XI are provided which are conformationally restricted by means of intramolecular bonding

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# PEPTIDE ANALOGS OF THE ACTIVATED PLATELET BINDING SITE ON FACTOR XI

## Field of the Invention

The invention relates to synthetic peptide analogs of factor XI heavy chain.

## Background of the Invention

Factor XI.

Human factor XI is a plasma glycoprotein that participates in the contact phase of blood coagulation. Fujikawa et al., Biochemistry 25, 2417-2424 (1986) (incorporated herein by reference) disclose the amino acid sequence of factor XI, deduced from the sequence of a cDNA insert coding for factor XI.

Factor XI circulates in plasma as a complex with its nonenzymatic cofactor, high molecular weight kininogen. The complex of factor XI and kininogen can become bound to an anionic surface, where factor XI can be activated by factor XIIa. An example of an anionic surface to which the complex can become bound is an activated platelet surface. When zinc ions are present, the complex binds specifically to high affinity, saturable receptors on activated platelets.

If factor XI of the complex becomes bound to an activated platelet, rates of factor XI activation by XIIa can

The heavy chain contains four tandem repeat sequences (designated A1, A2, A3 and A4), comprising four separate domains. Factor XIa of the complex remains bound to the activated platelet site and recognizes factor IX as its normal macromolecular substrate. Factor XIa catalyzes the activation of factor IX, which can lead to intrinsic coagulation.

Analysis of rates of factor IX activation by platelet-bound and unbound factor XIa indicates that these reaction rates are nearly identical. However, platelet-bound factor XIa is protected from inhibition by both plasma and platelet derived inhibitors.

Two inhibitors of factor XIa enzymatic activity in human plasma are the serpins, α-1-proteinase inhibitor and antithrombin III. Two other inhibitors are protease nexin II, which is a truncated form of the transmembrane Alzheimer's amyloid ß-protein precursor, and platelet inhibitor of factor XI (PIXI), which is a low molecular weight 8,500 Da protein from platelets. None of these four inhibitors significantly inhibit platelet-bound factor XI.

Activated factor IX (factor IXa) can be produced by factor XIa enzymatic activity and can bind to a factor IX/IXa binding site on the platelet surface. Importantly, the binding of factors IX/IXa and VIIIa to their respective sites on the platelet membrane results in a twenty million-fold acceleration in the catalytic efficiency of factor X activation. Thus, platelet surface-localized factor IX activation results in enhanced intrinsic coagulation results.

The activation of factor XI and sustained expression of its enzymatic activity at the platelet surface are key biological events in hemostasis. Moreover, the binding of factor XI to the platelet surface protects it from inactivation by both plasma and platelet derived inhibitors. Bound, activated factor XI will continue its protected enzymatic activity at the platelet surface irrespective of the presence of factor XIa inhibitors. Since high molecular weight kininogen is necessary for factor XI to be efficiently bound to platelets (Sinha, et al. J. Clin. Invest. 73 1550-1556, at page 1551, col. 2, ¶3, and page 1552, col. 2, ¶2 (1984)), it has been postulated that factor XI binds indi-

rectly to platelets through kininogen. See, Greengard et al. Biochem., 25, 3884-3890 (1986). The high molecular weight kininogen binding site on domain A1 of the factor XI heavy chain has been characterized by Baglia et al., J. Biolog. Chem. 267, 4247-4252 (1992); and Baglia et al., J. Biolog. Chem. 265, 4149-4154 (1990) (each incorporated herein by reference). A computer structural model useful for producing constrained peptides capable of inhibiting the binding of factor XI to high molecular weight kininogen, was also characterized. Artificially constrained peptides according to the computer model were synthesized, which correspond to amino acids 44 (Thr) to 86 (Ser) in the A1 domain of the intact factor XI heavy chain. See, Baglia et al. J. Biolog. Chem. 267, 4247-4252 (1992). The peptides are capable of inhibiting the binding of factor XI to high molecular weight kininogen. Examples of such peptides are SEQ ID NOS: 13, and 17-22.

Since high molecular weight kininogen is required for platelets to efficiently bind factor XI, it was not known prior to the present invention that a direct binding site for activated platelets exists in the heavy chain of factor XI. Also, the location of the site of interaction between the heavy chain of factor XI and the platelet surface has not been defined until the present invention.

Antithrombotic Therapy.

Existing methods of preventing or treating arterial and venous thrombosis involve inhibiting the blood coagulation cascade with oral anticoagulants, heparin or other anticoagulants, or alternatively by pharmacologically inhibiting platelets. For example, oral anticoagulants such as coumarin-like drugs are used to inhibit the synthesis of vitamin K-dependent proteins. They block many coagulation reactions, involving proteins such as prothrombin, factor VII, factor IX and factor X. Heparin, by potentiating the action of antithrombin III, accelerates inactivation of thrombin, factor Xa and a variety of other plasma serine proteases.

These therapeutic approaches are nonselective and inhibit coagulation reactions involved in the development of venous and arterial thrombosis while at the same time inhibiting reactions which are essential for the maintenance of normal hemostasis. Similarly, most platelet inhibitor drugs block a wide variety of platelet responses. Thus, while some drugs may be effective in preventing thrombotic processes, they can enhance the risk of bleeding. What is needed is a therapeutic agent which specifically interferes with intrinsic coagulation reactions leading to the activation of factors XI or IX, while leaving extrinsic coagulation reactions intact. This will permit normal hemostatic plug formation at sites of vascular injury, thereby minimizing the risk of bleeding during the antithrombotic therapy.

Prevention of factor XI binding to activated platelets would limit the biologically important platelet contribution to coagulation reactions. Accordingly, there is a need for antithrombotic agents which inhibit the binding of factor XI and/or factor XIa to surfaces of activated platelets.

## Summary of the Invention

A synthetic peptide is provided comprising an amino acid sequence corresponding to a portion of the sequence of the binding site for activated platelets on the heavy chain of XI. The peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to activated platelet surfaces.

In another embodiment, the invention is directed to a method of designing a peptide analog to the binding site for activated platelets on the factor XI heavy chain. The distance between two parts of a molecular model of the substrate binding site is determined at conformational equilibrium. The primary structure of the binding site is then modified to restrict that distance to the determined distance. A peptide comprising the modified primary structure is then synthesized.

In yet another embodiment of the invention, a method of producing a peptide having a restricted conformation is provided. Accordingly, a peptide having an amino acid sequence corresponding to a portion of the sequence of the binding site for activated platelets on the factor XI heavy chain is provided. The conformational equilibrium of that portion of the factor XI heavy chain is determined. A covalent modification is introduced into the peptide to restrict a distance between two parts of it to a distance between corresponding parts of the peptide in the equilibrium confirmation determined.

The invention further provides pharmaceutical compositions comprising one or more of the peptides according to the invention corresponding to a portion of the sequence of the binding site for activated platelets on the factor XI heavy chain, or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier. Preferred pharmaceutical compositions further comprise a second synthetic peptide having an amino acid sequence corresponding to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, or a pharmaceutically acceptable salt of the second peptide; wherein the second peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen.

The invention also provides a method of inhibiting the binding of factor XI to activated platelets and factor XIa-induced activation of factor IX on a platelet surface. The activated platelets are contacted with one or more peptides of the invention, corresponding to a portion of the sequence of the binding site for activated platelets on the factor XI heavy chain, which peptide competes with factor XI in the binding of the activated platelets. Activation of factor IX on the platelet surface is thus indirectly inhibited by the peptides of the invention. Inhibition of factor IX activation on the platelet surface in turn inhibits factor IX's coagulant activity. Thus, the peptides of the invention are potent anticoagulants, having antithrombotic utility.

A preferred method for inhibiting the binding of factor XI to activated platelets and preventing the factor XIa-induced activation of factor IX on a platelet surface also comprises contacting activated platelets with a second synthetic peptide corresponding to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, or a pharmaceutically acceptable salt of said peptide; wherein the second peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen.

By "platelet binding site" or "activated platelet binding site" on factor XI heavy chain is meant the region of the intact factor XI polypeptide chain comprising from about amino acid 193 (Ala) to about amino acid 266 (Arg) of the mature polypeptide, corresponding to amino acid 13 (Ala) to amino acid 86 (Arg) of SEQ ID NO:1.

By "high molecular weight kininogen binding site" on factor XI heavy chain is meant the region of the intact factor XI polypeptide chain comprising from about amino acid 44 (Thr) to about amino acid 86 (Ser) of the mature polypeptide, corresponding to SEQ ID NO:22.

By "sequence corresponds to a portion of an identified binding site" on the factor XI heavy chain is meant a sequence which comprises a sequence segment identical to a portion of the identifed binding site sequence or a sequence segment derived from a three-dimensional model of a portion of the identified binding site sequence.

## Description of the Figures

A3 Domain-Derived Peptides

Figure 1 is a graph showing the effect of synthetic factor XI domain A3-derived peptides according to the invention on the binding of radio labelled factor XI to activated platelets in the presence of $ZnCl_2$ (25 $\mu$M), $CaCl_2$ (2 mM), and high molecular weight kininogen (42 nM). The binding of $^{125}$I-factor XI was compared to control binding in the absence of competing peptides. The percentage of factor XI binding was then plotted against the concentration of the

synthetic peptide. The experimental protocol is set forth in detail in Example 13(d) below.

Figure 2 is a graph showing the effect of factor XI and synthetic factor XI heavy chain domain A1-, A2-, A3-, and A4-derived peptides on the binding of radiolabelled factor XI to activated platelets in the presence of $ZnCl_2$ (25 $\mu$M), $CaCl_2$ (2 mM), and high molecular weight kininogen (42 nM). The binding of $^{125}$I-factor XI was compared to control binding in the absence of competing XI or competing peptides. The percentage of factor XI binding was then plotted against the concentration of XI or the synthetic peptide. The experimental protocol is set forth in detail in Example 13(d) below.

## Detailed Description of the Invention

Four tandem repeat sequences (designated A1, A2, A3 and A4) comprising four separate domains, are present in the factor XI heavy chain. We have found that the platelet binding site on factor XI is located in the carboxy-terminal seventy-five residues of domain A3. The binding site consists of the sequence of amino acids Ala 193 to Arg 266 in the A3 domain. The sequence consists of anti-parallel $\beta$-strands connected by ß-turns, forming three stem-loop structures. We have found that these three stem-loop structures together form a continuous surface which is utilized for the binding of platelets. The deduction of the platelet binding site structure was accomplished by computer modeling to calculate a testable three-dimensional structure utilizing the primary amino acid sequence and disulfide linkages within the A3 domain. The calculated structure shows that the three stem-loop structure are defined by amino acid residues Pro 229 - Gln 233, Thr 241 - Leu 246 and Ser 248 - Ser 261, which correspond to SEQ ID NO:1, amino acids 49-53, 61-66, and 68-81, respectively.

The modeled A3 domain structure is used as a design template for synthesizing peptides according to the present invention that are expected to adopt a conformational repertoire overlapping that of the native protein. The sequences identified herein from the factor XI heavy chain

sequences identified herein from the factor XI heavy chain have not been previously identified as inhibitory of XI binding to platelets, and thus inhibitory of factor IX activation on the platelet surface. The peptides of the invention, which mimic the platelet binding site on factor XI and factor XIa, are potent inhibitors on the platelet surface of the enzymatic activity of factor XIa against its macromolecular substrate, factor IX. The peptides are potent anticoagulants, which are believed useful as antithrombotic agents.

Ideally, an antithrombotic agent should interfere with intrinsic coagulation reactions leading to the activation of factors XI and IX, while leaving extrinsic coagulation reactions intact, so that normal hemostatic plug formation can occur at sites of vascular injury. The peptides of the invention, by virtue of their specificity for the platelet binding site on factor XI/XIa, are believed to inhibit factor XIa-catalyzed factor IX activation on the surface of platelets, without affecting the extrinsic pathway of blood coagulation involving factors VII, X and V, and prothrombin. The inventive peptides' inhibition of platelet binding to factor XI and subsequent effect on activated partial thromboplastin time, without effect on prothrombin time, evidences their specificity for the intrinsic coagulation pathway. Thus, it is believed that the peptides inhibit or minimize intravascular thrombus formation without sacrificing normal hemostatic plug formation.

Traditional syntheses of the linear amino acid sequence of biologically interesting proteins may result in peptides that are either biologically inactive or, at best, marginally active. We have created a molecular model of the three-dimensional structure of factor XI heavy chain domain A3. The structure created in this manner is used as a template for designing conformationally-restricted synthetic analogs having the ability to inhibit the binding of factor XI and/or XIa to platelet surfaces and thus inhibit the factor XIa-induced activation of factor IX on the surface of platelets. Using both distance and geometric constraints imparted through measurements of the subdomains within the

calculated structure, constraints are artificially introduced, e.g., disulfide bonds, to limit the conformational freedom of a synthetic peptide that incorporates the relevant amino acids. Certain conformationally-restricted synthetic peptide analogs having the ability to inhibit the binding of factor XI or factor XIa to platelets correspond to factor XI heavy chain residues 225-236, 229-233, 241-246 and 248-261, according to the numbering of the amino acids of the mature polypeptide. The model disclosed herein may be utilized to prepare additional conformationally-restricted synthetic peptides having similar activity.

Appendix 1 included herein contains the set of Brookhaven coordinates and connect statements specifying our equilibrium conformation model of the major portion of factor XI heavy chain domain A3 comprising the 85 amino acids spanning positions Ala 181 to Cys 265, inclusive (SEQ ID NO:1, amino acids 1-85). The remaining amino acids of the A3 segment, Arg 266 and His 267 - Phe 272 (SEQ ID NO:16), of the factor XI heavy chain were truncated. The corresponding graphic molecular model satisfying these coordinates may b

two γ carbons of VAL 11 are designated "CG 1" and "CG 2" respectively.

The data file further comprises a connect statement which begins immediately after the coordinates for atom 771. The connect statement identifies the covalent bonding pattern of each of the 771 atoms. Thus, for example, the 68th entry of the connect statement (CONNECT 68) indicates that atom 68, which is the α carbon atom PRO 8 (corresponding to amino acid 188 of the mature factor XI heavy chain sequence), is bonded to atom 67 (the nitrogen of the same residue), atom 69 (the carbonyl carbon of the same amino acid residue), and atom 71 (the β carbon of the same amino acid residue). The complete data file of 771 coordinates, together with the connect statement for these entries, specifies the equilibrium conformation of factor XI heavy chain domain A3.

The peptides of the invention generally have an amino acid sequence similar to the native domain A3 sequence in the vicinity of the platelet binding site. However, a covalent modification is artificially introduced to restrict the analog to the conformation (or one close to it) displayed by the above model. Preferably, the synthetic peptides consist essentially of peptide having from at least five to about 80 amino acid residues, which peptide has a restricted conformation. Generally, the covalent modification is accomplished by determining a distance between two non-contiguous parts of the amino acid chain according to the model. Then a chemical moiety is introduced to fix that determined distance in the analog. For example, a 5-6A distance can be fixed using a disulfide bond. Cysteine residues can be introduced at the appropriate positions in the model and then the new cysteine-containing model is tested for its ability to mimic the structure observed in the model. Alternatively, the disulfide bond can be artificially introduced by generating a disulfide bond between native cysteine residues when this will produce a polypeptide with a restricted conformation corresponding to the above model.

In constraining the peptides it is sometimes necessary to compensate for the orientation of amino acid

side chains such that torsional stress does not misalign the peptide structure. Thus, in some instances, it is desirable to employ D-Cys analogs or appropriate combinations of D-L cysteines to mimic the correct stereochemistry. In general, these peptides are then synthesized according to the standard chemistry described below.

The use of native or artificially introduced cysteine residues to create the artificially introduced disulfide bridge is one way to conformationally restrict the peptides. Disulfide bonds, however, can be intrinsically unstable and it is sometimes difficult to obtain a homogeneous solution of intradisulfide-bonded species without concomitant mixed disulfides. If a biologically active conformationally restricted peptide having a cysteine-cysteine disulfide bond tends to unfold, it may be more effective to constrain the peptide in a folded conformation via a covalent bond which is more stable than a disulfide bridge. There are several strategies which can be utilized in the covalent closure of the peptides. Two of these strategies are described below.

The peptide can be internally cross-linked via the side chains of a lysine $\epsilon$-amino group and the carboxylic acid function of a glutamic or aspartic acid side chain, thus creating an amide bond. The peptide is synthesized according to standard procedures on a low substitution (0.2 mmol/gm or less) paramethylbenzhydrylamine resin. The first residue added to the resin is an N-$\alpha$-tBOC,$\epsilon$-fMOC lysine. The rest of the peptide synthesis is continued normally using tBOC chemistry until the final residue is added. The last residue to be added is a Z-protected glutamic acid, where the carboxylic acid moiety is protected with a tert-butyl group. Treatment of the peptide resin with piperidine/DMF removes the fMOC group from the $\epsilon$-amino group of the initial lysine without affecting any other protection groups. Subsequent treatment with trifluoroacetic acid removes the protection of the carboxylic acid group of the glutamic acid. Following neutralization, the peptide is covalently closed using a standard diimide-mediated coupling reaction. It should be

emphasized that this is only one of the ways in which the synthetic peptide can be covalently closed.

Other fMOC/tBOC strategies include covalent closure of the peptide between two free amino groups utilizing toluene-2,4-diisocyanate (TDI), a heterobifunctional cross-linker. The methyl group of the aromatic ring of TDI prevents the isocyanate group in the 2 position from reacting at a pH 7.5 or below, whereas the isocyanate group in the para position is highly reactive. A shift in pH to greater than 9.0 will initiate a reaction with the isocyanate group in the 2 position, thus enabling highly specific and controlled conditions for covalent closure of the peptide.

By utilizing a variety of different strategies for restricting the conformation of peptides, distance geometries and orientation of the folded peptide can be controlled. Any such strategies employing chemical reactions known in the art may be used.

Using these techniques, synthetic peptide analogs can be made and tested for their ability to inhibit factor XI binding to platelets and factor XIa-induced activation of factor IX on the platelet surface. Particularly useful peptide analogs which were derived using the techniques described herein comprise amino acids 181-265, 191-266, 193-199, 226-235, 229-233, 235-266, 241-246, 248-253 and 248-261 of the factor XI heavy chain.

The 181-265, 191-266 and 235-266 peptides have an amino acid sequence identical to segments of the native factor XI sequence, i.e., SEQ ID NO:1 amino acids 1-85 and 8-86, and SEQ ID NO:2, respectively. Each of the three peptides has at least one artificially introduced disulfide bond, i.e., between their cysteine residues corresponding to positions 242 and 265 in the factor XI mature polypeptide chain. The disulfide bond is artificially introduced in the peptide chain by a chemical reaction step after the synthetic peptide is made and purified.

The 193-199, 226-235, 229-233, 241-246 and 248-261 are identical in sequence to the corresponding sequence of native factor XI, except for two modifications in each molecule. In the 193-199 peptide, Ala 193 and Ser 199 were

replaced by cysteine residues to generate SEQ ID NO:12. This modified 193-199 peptide is designated "Ala 193(C) - Ser 199(C)" to distinguish it from the native 193-199 peptide. In each of the 226-235, 229-233, 241-246 and 248-261 peptides, the first-numbered and last-numbered amino acids were replaced by cysteine residues to generate SEQ ID NOS:11, 9, and 8, and D-Cys-(SEQ ID NO:7)-Cys, respectively. As in the designation of the modified 193-199 peptide, the modified peptides corresponding to each of the 226-235, 229-233, 241-246 and 248-261 peptides, are listed with their native first-numbered and last-numbered amino acids followed by a "(C)" to indicate that the native amino acids have been replaced by cysteine residues. The "(C)" after the amino acid number distinguishes the modified peptides from the native sequence peptides to which they correspond.

In the 248-253 peptide, Ser 248 was replaced by a cysteine residue, a glycine residue was inserted between amino acid Lys 252 and Lys 253, and Lys 253 was replaced by a cysteine residue to generate SEQ ID NO:10. This modified 248-253 peptide is designated "Ser 248(C) -Lys 253(G - C)" to distinguish it from the native 248-253 peptide.

All eight peptides were restricted conformationally using cysteine-cysteine disulfide bonds, but other restricting means may be advantageously used. Each peptide inhibits the activation of factor IX by factor XIa, and, as a consequence, may be used to inhibit the procoagulant function of factor XIa. Methods of assaying factor XI binding to platelets are known in the art. One such method is described hereinafter in Example 10(d).

The present peptides are relatively short in length and therefore they are easily synthesized by chemical means. Such synthetic peptides have many advantages over the use of the entire A3 domain, or the entire factor XI heavy chain. Large portions of the heavy chain cannot conveniently be made by synthetic techniques and must be made by recombinant DNA techniques, which are expensive and time consuming. Additionally, larger proteins may be insoluble, or may be immunogenic when introduced into a patient. Shorter synthet-

ic peptides may be more soluble and less immunogenic than larger proteins.

As used herein, "peptide" refers to a linear series of no more than about eighty (80) amino acid residues connected to one another by peptide bonds between the alpha-amino groups and carboxy groups of adjacent amino acid residues. Additional covalent bonds between portions of the peptide are also present to restrain the conformation of the molecule, such as amide and disulfide bonds. The term "synthetic peptide" means a chemically derived chain of amino acid residues linked together by peptide bonds that is free of naturally occurring proteins and fragments thereof.

The term "homology" as describing the relationship between two amino acid sequences means the extent to which the sequences, viewed from the N-terminal to the C-terminal direction, have segments of their sequences which are identical and which occur in the same N-terminal to C-terminal order in the overall sequence. The synthetic peptides according to the invention have an amino acid sequence which is the same as that of the native amino acid sequence, but for inserted, deleted, or interchanged (one or more amino acids is substituted for the same number of other amino acids) portions.

The degree of amino acid sequence homology between the amino acid sequence of a synthetic peptide according to the invention and that of the native peptide is expressed as a percentage. This percentage is obtained by determining the number of amino acids in the sequence of the synthetic peptide which occur in segments that are identical to segments of the native amino acid sequence and which occur in the same N-terminal to C-terminal order as the native segments, divided by the total number of amino acids in the native sequence.

A "substantial amino acid sequence homology" is any amino acid sequence homology greater that 30 percent. Preferably the homology is greater than 80 percent, most preferably greater than 90 percent.

Peptides of the present invention include any analog, fragment or chemical derivative of the peptides capable of inhibiting the binding of factor XI and/or XIa binding to

platelets. The term "analog" includes any peptide having substantial amino acid sequence homology to the peptides of the invention in which one or more amino acids have been substituted with other amino acids, and the substituted amino acids allow or require the peptide to assume the equilibrium conformation of the domain of the parent protein. Often, cysteine, lysine and glutamic acid will be used for their side chains which can form covalent linkages to restrict the conformation of a peptide. In addition, conservative amino acid changes may be made which do not alter the biological function of the peptide. For instance, one polar amino acid, such as glycine, may be substituted for another polar amino acid; or one acidic amino acid, such as aspartic acid may be substituted for another acidic amino acid, such as glutamic acid; or a basic amino acid, such as lysine, arginine or histidine may be substituted for another basic amino acid; or a non-polar amino acid, such as alanine, leucine or isoleucine may be substituted for another non-polar amino acid.

The term "analog" shall also include any peptide which has one or more amino acids deleted from or added to an amino acid sequence identical to that of native fragment of the amino acid sequence of factor XI heavy chain domain A3, but which still retains a substantial amino acid sequence homology to the platelet binding site on factor XI or factor XIa, as well as the ability to inhibit the binding of platelets to factor XI or factor XIa.

The term "fragment" shall refer to any shorter version of the peptides identified herein having at least five amino acid residues, wherein the fragment is a synthetic peptide which is capable of inhibiting the binding of platelets to factor XI or factor XIa.

The three-letter symbols used to represent the amino acid residues in the peptides of the present invention are those symbols commonly used in the art. The amino acid residues are preferred to be in the "L" isomeric form. However, residues in the "D" isomeric form may be substituted for any L-amino acid, as long as the desired functional property of inhibition of factor XIa-induced factor IX activation is retained by the peptide. The three-letter symbols used

herein refer to the following amino acids: Ser is serine; Ile is isoleucine; Gln is glutamine; Phe is phenylalanine; His is histidine; Trp is tryptophan; Lys is lysine; Asn is asparagine; Leu is leucine; Gly is glycine; Thr is threonine; Asp is aspartic acid; Arg is arginine; and Ala is alanine.

The peptides of the present invention may be prepared by any of the following known techniques. Conveniently, the peptides may be prepared using the solid-phase synthetic technique initially described by Merrifield, in J. Am. Chem. Soc. 15, 2149-2154 (1963). Other peptide synthesis techniques may be found, for example, in M. Bodanszky et al., Peptide Synthesis, John Wiley & Sons, 2d Ed. (1976); Kent and Clark-Lewis in Synthetic Peptides in Biology and Medicine, eds. Alitalo, K., Partanen, P. and Vakeri, A., (Elsevier Science Publishers, Amsterdam, 1985) p. 295-58; as well as other reference works known to those skilled in the art. A summary of peptide synthesis techniques may be found in J. Stuart and J.D. Young, Solid Phase Peptide Synthelia, Pierce Chemical Company, Rockford, IL (1984). The synthesis of peptides by solution methods may also be used, as described in The Proteins, vol II, 3d Ed., Neurath, H. et al., Eds., p. 105-237, Academic Press, New York, NY (1976). Appropriate protective groups for use in such syntheses will be found in the above texts as well as in J. F. W. McOmie, Protective Groups in Organic Chemistry, Plenum Press, New York, NY (1973). Of course, the present peptides may also be prepared by recombinant DNA techniques. But, such methods are not preferred because of the need for purification and subsequent chemical modifications to conformationally restrain the peptides.

In general, these synthetic methods involve the sequential addition of one or more amino acid residues or suitably protected amino acid residues to a growing peptide chain. Normally, either the amino or carboxyl group of the first amino acid residue is protected by a suitable, selectively-removable protecting group. A different, selectively-removable protecting group is utilized for amino acids containing a reactive side group, such as lysine.

Using a solid phase synthesis as an example, the protected or derivatized amino acid is attached to an inert solid support through its unprotected carboxyl or amino group. The protecting group of the amino or carboxyl group is then selectively removed and the next amino acid in the sequence having the complementary (amino or carboxyl) group suitably protected is admixed and reacted under conditions suitable for forming the amide linkage with the residue already attached to the solid support. The protecting group of the amino or carboxyl group is then removed from this newly added amino acid residue, and the next amino acid (suitably protected) is then added, and so forth. After all the desired amino acids have been linked in the proper sequence, any remaining terminal and side group protecting groups (and solid support) are removed sequentially or concurrently, to provide the final peptide. The peptides of the invention are devoid of benzylate or methylbenzylated amino acids. Such protecting group moieties may be used in the course of synthesis, but they are removed before the peptides are used. Additional reactions may be necessary, as described elsewhere, to form intramolecular linkages to restrain conformation.

The A3 domain-derived peptides of the present invention generally contain at least five (5) amino acid residues and up to eighty (80) amino acid residues, preferably from about five (5) to about forty-five (45) amino acid residues, and as small as about five (5) to about twenty (20) amino acids. These peptides may be linked to an additional sequence of amino acids either or both at the N-terminus and at the C-terminus, wherein the additional sequences are from 1-100 amino acids in length. Such additional amino acid sequences, or linker sequences, can be conveniently affixed to a detectable label or solid matrix, or carrier. Typical amino acid residues used for linking are tyrosine, cysteine, lysine, glutamic acid and aspartic acid, or the like.

As described above, the A3 domain-derived peptides according to the invention directly inhibit the binding of platelets to factor XI or factor XIa by competing with factor XI for binding sites on the platelet surface. Furthermore,

high molecular weight binding to factor XI has been observed to insure the efficiency of factor XI binding to platelets, Sinha, et al. J. Clin. Invest. 73 1550-1556, at 1552, col. 2, ¶2 (1984). Factor XI heavy chain A1 domain-derived peptides, are known to inhibit the binding of factor XI or factor XIa to high molecular weight kininogen, thereby indirectly inhibiting the binding of factor XI/XIa to the platelet surface. A3 domain-derived peptides of the invention may be combined with A1 domain-derived peptides to provide a dual effect.

The dual effect is attained when platelets are treated with A3 domain-derived peptides and high molecular weight kininogen is treated with A1 domain-derived peptides prior to adding factor XI/XIa to the platelets and kininogen. The A3 domain peptides directly inhibit factor XI/XIa binding to platelets by competing with intact factor XI/XIa. The A1 domain-derived peptides indirectly inhibit factor XI/XIa binding to platelets by inhibiting high molecular weight kininogen binding to factor XI/XIa.

A1 Domain-Derived Peptides

Baglia et al., J. Biolog. Chem. 267, 4247-4252 (1992); and Baglia et al., J. Biolog. Chem. 265, 4149-4154 (1990) have characterized the high molecular weight kininogen binding site on the domain A1 of the factor XI heavy chain. A computer structural model useful for producing constrained peptides capable of inhibiting the binding of factor XI and high molecular weight kininogen and examples of peptides which compete with factor XI for binding to kininogen were described. Artificially constrained synthetic peptides corresponding to amino acids 44 (Thr) to 86 (Ser) of the intact factor XI heavy chain and constrained active analogs, which are capable of inhibiting the binding of factor XI and high molecular weight kininogen by competing with factor XI for binding to kininogen, were also characterized. Examples of such peptides which inhibit the binding of factor XI and high molecular weight kininogen have amino acid sequences as set forth in SEQ ID NOS: 13, and 17-22.

The modeled A1-domain structure is used as a design template for synthesizing peptides that are expected

to adopt a conformational repertoire overlapping that of the native protein in the same manner as described for the modeled A3-domain structure. The model for the A1-domain structure disclosed herein may be utilized to prepare additional conformationally-restricted synthetic peptides having similar activity to the A1-domain derived synthetic peptides described above. Such synthetic A1-domain derived conformationally restricted peptides may be prepared, modified and constrained in essentially the same manner as described above for the A3 domain-derived peptides according to the invention.

Appendix 2 included herein contains the set of Brookhaven coordinates and connect statements specifying the equilibrium conformation model of Baglia et al., J. Biolog. Chem. 267, 4247-4252 (1992) (incorporated herein by reference) which characterizes the structure of the high molecular weight kininogen binding site corresponding to amino acids 44 (Thr) to 85 (Ser) of the intact factor XI heavy chain. The major portion of factor XI heavy chain domain A1 comprising the 85 amino acids spanning positions Glu 1 to Cys 85, inclusive (SEQ ID NO:23) is utilized. The corresponding graphic molecular model satisfying these coordinates may be generated by inputting the coordinates and connect statement into any of the many commercially available molecular modeling programs which are capable of reading files in the Brookhaven format.

The A1 domain-derived peptide is preferably a synthetic peptide comprising an amino acid sequence from at least five to about fifty amino acids in length, which corresponds to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI. The A1 domain-derived peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen. Particularly preferred A1 domain-derived peptides comprise at least one amino acid sequence selected from the group consisting of SEQ ID NO:13 and SEQ ID NOS: 17-22.

Preferably the restricted conformation of the A1 domain-derived peptide is determined from the equilibrium

conformation model comprising the set of coordinates and connect statements of Appendix 2. The restricted conformation may be provided in the same manner as for the A3 domain-derived peptides.

Pharmaceutical Salts of Peptides

The A3 domain-derived peptide of the present invention and the A1 domain-derived peptide may be used in the form of a pharmaceutically acceptable salt. Suitable acids which are capable of forming salts with the peptides include inorganic acids such as hydrochloric acid, hydrobromic acid, perchloric acid, nitric acid, thiocyanic acid, sulfuric acid, phosphoric acid and the like; and organic acids such as formic acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, malonic acid, succinic acid, maleic acid, fumaric acid, anthranilic acid, cinnamic acid, naphthalene sulfonic acid, sulfanilic acid or the like.

Suitable bases capable of forming salts with the peptides include inorganic bases such as sodium hydroxide, ammonium hydroxide, potassium hydroxide and the like; and organic bases such a mono-, di- and tri-alkyl and aryl amines (e.g., triethylamine, diisopropyl amine, methyl amine, dimethyl amine and the like) and optionally substituted ethanol-amines (e.g., ethanolamine, diethanolamine and the like).

Pharmaceutical Compositions

For use in a method of treatment, such as treatment for inhibiting the binding of platelets to factor XI or XIa and/or inhibiting the coagulant activity of factor XIa on the platelet surface, one or more of the synthetic A3 domain derived peptides of the present invention may be present in a pharmaceutical composition in admixture with a pharmaceutically acceptable carrier.

Preferred pharmaceutical compositions for inhibiting the binding of platelets to factor XI or factor XIa in a mammal also include a second peptide which inhibits the binding of factor XI or factor XIa to high-molecular weight kininogen to inhibit the binding of factor XI or factor XIa

to the platelet surface. The second peptide is an artificially constrained A1 domain-derived synthetic peptide as described above.

The pharmaceutical composition may be compounded according to conventional pharmaceutical formulation techniques. The carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., sublingual, rectal, nasal, oral or parenteral. Compositions for oral dosage form may include any of the usual pharmaceutical media, such as, for example, water, oils, alcohols, flavoring agents, preservatives, coloring agents and the like in the case of oral liquid preparations (e.g., suspensions, elixirs and solutions) or carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations (e.g., powders, capsules and tablets). Controlled release forms may also be used. Because of their ease in administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques.

For compositions to be administered parenterally, the carrier will usually comprise sterile water, although other ingredients to aid solubility or for preservation purposes may be included. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like may be employed. The parenteral routes of administration may be intravenous injection, intramuscular injection or subcutaneous injection.

For intravenous administration, the peptides may be dissolved in an appropriate intravenous delivery vehicle containing physiologically compatible substances such as sodium chloride, glycine and the like, having a buffered pH compatible with physiologic conditions. Such intravenous delivery vehicles are known to those skilled in the art.

It is contemplated that the A3 domain-derived peptides of the present invention, both alone or in combination with the A1 domain-derived peptides, have utility as

anticoagulant and/or antithrombotic agents. It is contemplated that the A3 domain-derived peptides, both alone or in combination with the A1 domain-derived peptides, may be administered to patients either at risk for developing arterial or venous thrombosis, or to patients with established thromboembolism to prevent extension of the thrombi. For example, it is contemplated that the A3 domain-derived peptides and optionally the A1 domain-derived peptides may find utility in the prevention and treatment of deep venous thrombosis and pulmonary embolism, treatment and prevention of cerebral vascular thromboembolism, the treatment and prevention of systemic arterial thrombosis and embolism, and the treatment and possibly the prophylaxis of established disseminated intravascular coagulation. Patients suffering from transient ischemic attacks are, in particular, at increased risk of brain damage through thrombus formation.

In particular, it is contemplated that the synthetic peptides will find utility in the prevention of rethrombosis following lytic therapy. While lytic agents such as tissue plasminogen activator, urokinase and streptokinase have been utilized to dissolve vascular thrombi, their use is associated with a significant rate of rethrombosis, about 20-30%. This is because lytic therapy results in the exposure of a thrombogenic site, at the location of the prior thrombus. While lytic agents are effective in dissolving vascular thrombi, they offer no protection from clot reformation. The A3 domain-derived peptides of the present invention, alone or in combination with the A1 domain-derived peptides are expected to possess substantial rethrombosis inhibiting activity, by virtue of their inhibition of the binding of platelets to factor XI or factor XIa and thus inhibition of factor XIa-induced activation of factor IX on the platelet surface, are expected to possess substantial rethrombosis inhibiting activity. The peptides may thus be administered as an adjuvant to lytic therapy to prevent reformation of dissolved vascular thrombi.

The A3 domain-derived type and A1 domain-derived peptides, which respectively directly and indirectly inhibit the binding of factor XI/XIa to a platelet surface, may be

administered by any convenient means which will result in the delivery of each peptide type to the bloodstream in an amount effective to inhibit the binding of factor XI and/or factor XIa to platelets. Intravenous administration is presently contemplated as the preferred administration route. The amount administered will depend on the activity of the particular compound administered, which may be readily determined by those of ordinary skill in the art. The amount may also vary depending on the nature and extent of the lesion which is to be protected from rethrombosis; the size and weight of the patient; the route of administration, the age, sex and health of the patient; and other factors. Generally, the A3 domain-derived and A1 domain-derived peptides may each be administered in an amount sufficient to individually or collectively provide a plasma concentration in the range of from about $10^{-9}$ to about $10^{-5}$ M, more preferably in the range of from about $1 \times 10^{-8}$ to about $5 \times 10^{-6}$ M. Plasma concentrations higher or lower than these may be utilized, depending upon the activity of the particular compound being administered, and the nature of the treatment.

It may be appreciated that a single bolus injection of 1 mg of each of the two types of peptides per kilogram of treated subject body weight would achieve a maximum in vivo plasma concentration of 100 nM for each peptide type, assuming 100% recovery of drug. It is therefore contemplated that bolus administration will comprise a dosage of from about 0.1 mg to about 1 gram of each peptide type, per kilogram subject body weight. The bolus administration is most advantageously followed by a continuous infusion of each type of peptide, or a mixture of the two types of peptides, as needed. The amount of each peptide type continuously infused depends on the approximate half-life of that peptide in the circulation. Those skilled in the art would, for any factor XI- or factor XIa- platelet-binding-inhibiting peptide and for any peptide inhibiting heavyweight kininogen binding to factor XI or factor XIa, be able readily to determine the half-life from routine experimentation.

Therefore, a preferred method for inhibiting thrombosis comprises administering to a mammal in need of such treatment an effective amount of

i) an A3 domain-derived synthetic peptide according to the invention corresponding to a portion of the sequence of the binding site for activated platelets on the factor XI heavy chain, which has an artificially restricted conformation and the ability to compete with factor XI in the binding of the activated platelets, or a pharmaceutically acceptable salt of said A3 domain-derived peptide; and

ii) an A1 domain-derived synthetic peptide corresponding to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, which A1 domain-derived peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen, or a pharmaceutically acceptable salt of said A1 domain-derived peptide.

The A3 domain-derived peptides of the invention, either alone, or in combination with an A1 domain-derived peptide, inhibit the activated partial thromboplastin time without affecting the prothrombin time. According to one exemplary treatment protocol, an amount of each of the A3 domain-derived peptide and A1 domain-derived peptide, shown effective by the in vitro assay described elsewhere herein, is administered to a patient by bolus administration and/or continuous infusion. The potency of each peptide, or the combination, and its clearance from the circulation is then monitored by drawing blood samples at timed intervals and assaying the patient's partial thromboplastin time. At the end of the evaluation period, the dosage of each peptide is adjusted to provide the desired in vivo effect.

The following non-limiting examples serve to illustrate the practice of the invention.

## Example 1

### Computer Model

A structural model of the A3 domain (residues Ala 181-Arg 266) was constructed using the computational chemis-

try package supplied by Molecular Simulations, Inc., Pasadena CA and a Silicon Graphics 4D 280 Parallel Processing Supercomputer. A description of the modeling package and methods has been previously published (Jameson, Nature 349, 465-466 (1989)). The A3 domain was prematurely truncated at Cys 265 because residues Arg 266 and His 267 - Phe 272 (SEQ ID NO:16) comprise a short connecting peptide not expected to contribute to either the conformation or the function of the A3 domain. Information concerning cysteine disulfide constraints was used to initiate model building, after which extended energy minimization calculations were carried out. Ten picosecond high energy (900°K) dynamic runs (energy-dependent simulations of molecular motion) were used to dislodge inappropriate amino acid contacts. The structure was allowed to cool to 300°K over a 100 picosecond dynamics calculation, followed by minimization of the resulting structure. A trajectory file, recorded over the entire dynamics run, indicated that after ~55 picoseconds of dynamics, the calculated backbone structure had stabilized, i.e., reached a low energy well. Since a disulfide-bonded cysteine has an ideal bond length from $\alpha$-carbon to $\alpha$-carbon of ~5-6Å, we searched the region between the $\beta$-stranded pairs (the stem portion of the stem-loop) for ideal disulfide distances as well as for locations where a disulfide bond would not be expected to induce torsional stress. The calculated structure shows 3 stem-loop structures defined by amino acid residues Pro 229 - Gln 233, Thr 241 - Leu 246, and Ser 248 - Ser 261.

**Examples 2-3**

Ala 181-Arg 266 and Asn 235-Arg 266 Peptides

The model structure of Appendix 1 was used as a design template in the construction of conformationally restricted peptides corresponding to factor XI heavy chain residues 181-266 (SEQ ID NO:1) and 235-266 (SEQ ID NO:2). An intrachain disulfide bond between the cysteine residues at positions 242 and 265 was allowed to form in the computer-assisted model. The predicted folding pattern of the putative structure was tested for its ability to mimic the structure

observed in our model of domain of A3. Finding satisfactory agreement, the peptides were synthesized according to conventional solid phase procedures on an Applied Biosystems 430A peptide synthesizer by a modification of the procedure described by Kent and Clark-Lewis in Synthetic Peptides in Biology and Medicine, eds. Alitalo, K., Partanen P., and Vakeri, A. (Elsevier Science Publishers, Amsterdam (pp. 29-58 (1985)), in which dimethyl formamide replaced methylene chloride in the routine wash cycles. The synthesis was carried out using a paramethylbenzhydrylamine resin (United States Biochemical Corp., Cleveland, OH). The solvents and protected amino acids were synthesis grade biotechnology products purchased from Fischer Scientific Co., Pittsburgh, PA. The resulting peptide was refolded by dissolving it in deionized water as a 0.1 mg/ml solution in a flask containing a stir bar. The pH was adjusted to 8.5 with $NH_4OH$ and the solution was allowed to stir at 5°C for at least three days. The resulting solution was lyophilized.

The folded peptides were examined by both reverse phase and gel filtration high performance liquid chromatography (HPLC). The HPLC system was the Waters 600 Gradient Module, Model 740 Data Module, Model 46K Universal Injector and Lambda-Max Model 481 Detector. Reverse phase chromatography was performed using a Waters C8 μBondapak Column equilibrated with 0.1% (V/V) trifluoroacetic acid. The column was eluted with a linear gradient of aqueous acetonitrile containing 0.1% trifluoroacetic acid with a detector set at a wavelength of 220 nm. Gel filtration of the peptides was also carried out using a Waters Protein-Pak 60 column which was run isocratically with 0.1% (V/V) trifluoroacetic in 20% acetonitrile. Each of the two folded peptides demonstrated a single homogenous peak with a retention time identical to the corresponding unfolded peptide. This indicates the presence of a single homogeneous mixture for each refolded peptide, and not a mixed population of diverse polymers.

**Example 4**

Ser 248(C)-Ser 261(C) Peptide.

Following the procedures of Example 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 248-261 was modeled and prepared, except that the amino acid residues Ser 248 and Ser 261 of the native peptide were replaced with cysteine residues. The resulting modified peptide, Ser 248(C)-Ser 261(C), had the amino acid sequence of D-Cys-(SEQ ID NO:7)-Cys. The peptide was "refolded" to assume its correct conformation, as described in Examples 2-3.

Alternatively, the peptide was reduced with dithiothreitol and alkylated with iodoacetamide as previously described by Sinha et al., J. Biol. Chem. 260, 10714-10719 (1985). The chromatography results were the same after reduction and alkylation of the peptide, that is, a single peak with retention times identical to the original peptide was observed upon both reverse phase and gel filtration HPLC. The reduced/alkylated and corresponding refolded peptides were examined for free SH groups using the Ellman reagent, 5, 5'-dithiobis[2-nitro-benzoic acid]. It was determined that there was less than 0.02 mole of free SH per mole of peptide, which further verifies that the refolded peptide was a homogenous preparation consisting of the intramolecular disulfide-bonded peptide.

## Example 5

### Thr 241(C)-Leu 246(C) Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 241-246 was modeled and prepared, except that Thr 241 and Leu 246 were both replaced by Cys residues. The modified peptide, Thr 241(C)-Leu 246(C), thus had the amino acid sequence of SEQ ID NO:8.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to

disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 6**

Pro 229(C)-Gln 233(C) Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 229-233 was modeled and prepared, except that Pro 229 and Gln 233 were both replaced by Cys residues. The modified peptide, Pro 229(C)-Gln 233(C), thus had the amino acid sequence of SEQ ID NO:9.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 7**

Gln 226(C)-Asn 235(C) Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 226-235 was modeled and prepared, except that Gln 226 and Asn 235 were both replaced by Cys residues. The modified peptide, Gln 226(C)-Asn 235(C), thus had the amino acid sequence of SEQ ID NO:11.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 8**

Ala 193(C)-Ser 199(C) Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 193-199 was modeled and prepared, except that Ala 193 and Ser 199 were both replaced by Cys residues. The modified peptide, Ala 193(C)-Ser 199(C), thus had the amino acid sequence of SEQ ID NO:12.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 9**

Ser 248(C)-Lys 253(G-C) Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 248-253 was modeled and prepared, except that Ser 248 was replaced with a Cys residue, a glycine residue was inserted between Lys 252 and Lys 253, and Lys 253 was replaced by a Cys residue. The modified peptide, Ser 249(C)-Lys 253(G-C), thus had the amino acid sequence of SEQ ID NO:10.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 10**

Val 191 - Arg 266 Peptide

Following the procedure of Examples 1-3, a synthetic peptide corresponding to factor XI heavy chain residues 191-266 was modeled and prepared. The peptide, Val 191 - Arg 266, thus had the amino acid sequence of SEQ ID NO:1, amino acids 11-86.

The refolded peptide and the corresponding reduced/alkylated preparation were again found to have identical retention times by gel filtration and reverse phase HPLC. Moreover, the refolded peptide, as well as the reduced/alkylated peptide, were devoid of free thiols, thus confirming that all free SH groups were either oxidized to disulfides during the refolding procedure, or were reduced and alkylated during alkylation treatment.

**Example 11**

Synthesis of Heavy-Chain A1-domain Derived Peptides

Peptides corresponding to the A1-domain high molecular weight kininogen binding site in the factor XI heavy chain were synthesized and conformationally constrained in the same general manner as set forth in Examples 1-3. However, the model structure as provided by Baglia et al., J. Biolog. Chem. 267, 4247-4252 (1992), corresponding to the A1 domain was used as a design template instead of the A3 domain. The A1-domain derived peptides were conformationally restricted peptides corresponding to factor XI heavy chain high molecular weight kininogen binding site. The peptides produced have an amino acid sequence according to SEQ ID NOS:13 and 17-22.

**Example 12**

Heavy-Chain A2-domain and A4-domain Derived Peptides

Comparative peptides corresponding to the A2-domain segment (SEQ ID NO:14) and to the A4-domain segment (SEQ ID NO:15) in the factor XI heavy chain were synthesized in the same general manner as set forth in Examples 2-3, except that no three-dimensional modeling was attempted. The peptides were conformationally constrained by introducing

cysteine-cysteine disulfide bonds between the native cysteines.

## Example 13

### Effect of Heavy-Chain Derived Peptides on the Binding of Factor XI to Platelets

#### A. Purification of Human Coagulation Proteins.

Factor XI (specific activity 250 U/mg of protein) was purified from human plasma by immunoaffinity chromatography using a monoclonal antibody to factor XI (Sinha et al., J. Biol. Chem. 260, 10714-10719 (1985)).
High molecular weight kininogen (specific activity 15 U/mg) was purified by the method of Kerbiriou et al. (J. Biol. Chem. 254, 12020-12027 (1979)). Factor XI and high molecular weight kininogen were assayed by minor modifications (Scott et al., Blood 63, 42-50 (1984)) of the kaolin-activated partial thromboplastin time (Proctor et al., Am. J. Clin. Pathol. 36, 212-219 (1961)). All purified proteins appeared homogeneous by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

#### B. Radiolabeling

Purified XI was labeled with $^{125}I$ by a minor modification (Sinha et al., J. Biol. Chem. 260, 10714-10719 (1985)) of the iodogen method to a specific activity of $5 \times 10^6$ cpm/mg. The radiolabeled protein retained >90% of its biological activity compared with unlabeled factor XI.

#### C. Assay of Factor XI Binding to Platelets

All incubations were performed at 37°C without stirring the reaction mixture. Platelets were prewarmed and incubated at a concentration of (2-3) $\times 10^8$/mL in calcium-free HEPES-Tyrodes buffer, pH 7.3, in a 1.5 mL Eppendorf plastic centrifuge tube with a mixture of radiolabeled and unlabeled factor XI, $CaCl_2$ (2 mM), $ZnCl_2$ (25 $\mu$M), thrombin (0.1 U/ml) and high molecular weight kininogen (42 nM) or other proteins. At various times after the addition of the platelet stimulus, aliquots were removed and centrifuged through a

mixture of silicone oils as described (Greengard et al., Biochem., 25, 3884-3890 (1986)). Total binding was not corrected for any nonsaturable component. More than 86% of the platelets were sedimented under these conditions.

D. Effect of Peptides on Factor XI-Platelet Binding.

Platelets were incubated with $ZnCl_2$ (25 $\mu$M), $CaCl_2$ (2 mM), thrombin (0.1 U/ml) and high molecular weight kininogen (42 nM), and $^{125}$I-factor XI (0.025 $\mu$g/mL) and then mixed with various concentrations of A1-, A2-, A3- or A4- derived synthetic peptides, factor XI or buffer. After 20 minutes, samples were centrifuged. Binding of $^{125}$I-factor XI was compared to control binding in the absence of competing proteins.

The $I_{50}$ method of Cha, Biochem. Pharmacol. 24, 2177-2185 (1975) was used to determine the inhibitor constants as previously described (Sinha et al., Biochem. 26, 3768-3775 (1987)). In the case of classical competitive inhibition, $IC_{50}$ (total inhibitor concentration at which the enzyme reaction velocity is 50% of the uninhibited reaction) is related to the substrate concentration as follows,

$$I_{50} = 1/2\ Et + K_i + K_iS/K_m$$

where Et equals the total enzyme concentration and S equals the substrate concentration. $K_i$ was thus determined from the plot of $I_{50}$ vs S. The results are set forth in Table 1:

TABLE 1

| Competing Factor XI or Heavy Chain Peptide | $K_i$ of Peptide Inhibition of Factor XI Binding to Platelets |
|---|---|
| 1. Factor XI | $5.0 \times 10^{-8}$ |
| 2. Asn 235-Arg 266 (A3 Domain) (SEQ ID NO:2) | $7.0 \times 10^{-8}$ |
| 3. Phe 56-Ser 86 (A1 Domain) (SEQ ID NO:13) | $6.0 \times 10^{-6}$ |
| 4. Ala 134-Ala 176 (A2 domain) (SEQ ID NO:14) | NE* |
| 5. Ala 317-Gly 350 (A4 domain) (SEQ ID NO:15) | NE* |
| 6. Ser 248(C)-Ser 261(C) (A3 Domain) (D-Cys-(SEQ ID NO:7)-Cys) | $3.0 \times 10^{-4}$ |
| 7. Pro 229(C)-Gln 233(C) (A3 Domain)(SEQ ID NO:9) | $1.0 \times 10^{-3}$ |
| 8. Thr 241(C)-Leu 246(C) (A3 Domain)(SEQ ID NO:8) | $3.0 \times 10^{-3}$ |

* NE = No effect at concentrations up to $10^{-2}$ M

The $K_i$ of XI is included in Table 1 for comparison. The factor XI A3 peptide Asn 235 - Arg 266 of SEQ ID NO:2 is a potent inhibitor of factor XI binding to platelets in the presence of high molecular weight kininogen, $CaCl_2$, and $ZnCl_2$. The Ki is about 10 nM which is almost identical to the Ki for factor XI binding to platelets (See Table 1). In addition, the three peptides designed from the computer model of the A3 domain all have inhibitory activity in the binding assay.

By comparison peptides from the A2 domain, e.g., Ala 134-Ala 176 (SEQ ID NO:14) and from the A4 domain, e.g., Ala 317-Gly 350 (SEQ ID NO:15), have no effect upon the binding of factor XI to platelets. A peptide from the A1 domain, i.e., Phe 56-Ser 86 (SEQ ID NO:13), is an indirect but potent inhibitor of factor XI binding to platelets. The A1 domain peptide inhibits the binding of factor XI to high molecular weight kininogen, which is essential to promote

factor XI binding to a platelet receptor. Thus, the inhibition of factor XI binding to platelets by the A1 peptides is an indirect inhibition since the A1 peptides do not directly compete with factor XI for a binding site on the platelet surface. Conversely, the A3 peptides directly compete with factor XI for the binding site on the platelet surface.

Thus, the major binding site for platelets is located on factor XI A3 domain within residues Asn 235-Arg 266.

E. Synergism Between Ser 248(C)-Ser 261(C) Peptide and Folded Peptides from First and Second Stem Loops

The above factor XI binding of platelets assay was repeated with a mixture comprising equimolar amounts of the three peptides: Ser 248(C)-Ser 261(C), (D-Cys-(SEQ ID NO:7)-Cys); Pro 229(C)-Gln 233(C), (SEQ ID NO:9); and Thr 241(C)-Leu 246(C), (SEQ ID NO:8). These peptides added together showed mild synergism.

## Example 14

### Effect of A3-Derived Peptides on Coagulant Activity

Factor XI heavy chain peptides were assayed for inhibitory effects on blood coagulation. The activated partial thromboplastin time was measured in the presence of activated platelets or phospholipids. Since phospholipids can substitute for platelets in most coagulation reactions, parallel assays were run with the peptides to determine whether their inhibitory effects were specific for their interaction of platelets.

Factor XI activity was assayed the method of Scott et al., Blood 63, 42-50 (1984), with minor modifications. The assay determines the kaolin-activated partial thromboplastin time (Proctor et al., Am. J. Clin. Pathol. 36, 212-219 (1961)) using factor XI congenitally deficient substrate plasma. Coagulation mixtures containing kaolin, phospholipids or thrombin-activated platelets and factor XI deficient plasma were incubated at 37°C for five minutes in the presence of factor and various concentrations of the synthet-

ic peptides. The assay results were quantitated on double logarithmic plots of clotting times vs. concentrations of pooled normal plasma.

The A1 domain contains a binding site for high molecular weight kininogen, the A2 domain contains a substrate binding site for factor IX, and the A4 domain contains a binding site for factor XIIa. The peptides representing these respective binding sites showed inhibitory effects on intrinsic coagulation in the presence of both phospholipids and platelets, as manifested by the activated partial thromboplastin times.

By contrast, an A3 domain derived peptide according to the invention, e.g., Asn 235-Arg 266 (SEQ ID NO:2), was shown to be significantly inhibitory (Ki of about $2 \times 10^{-6}$ M) only in the presence of activated platelets. A 100-fold higher concentration of Asn 235-Arg 266 (SEQ ID NO:2) was required to demonstrate a similar inhibitory effect in the presence of phospholipids.

The parallel results indicate the specificity of the A3-derived peptides according to the invention for binding to platelets, and not to phospholipids.

**Example 15**

Effect of Mixtures of A1- and A3-Derived Peptides on Coagulant Activity

The factor XI heavy chain A1- and A3- derived artificially constrained peptides Phe 56 - Ser 86 (SEQ ID NO:13) and Asn 235 - Arg 266 (SEQ ID NO:2) are assayed for cumulative and synergistic effects by repeating the factor XI binding of platelets assay according to Example 13(d) with a mixture comprising equimolar amounts of the two peptides. Thus, the mixture is assayed for possible inhibitory effects on blood coagulation. The activated partial thromboplastin time is assessed in the presence of activated platelets or phospholipids. The inhibitory effect on intrinsic coagulation is greater in the presence of platelets than in the presence of phospholipids. This assay indicates the cumulative and synergistic anticoagulant effects of mixtures of

constrained A1-domain and A3-domain peptides, which peptides respectively correspond to the high molecular weight kininogen and platelet binding sites on factor XI.

All references with respect to synthetic, preparative and analytic procedures are incorporated herein by reference.

The present invention may be embodied in other specific forms without departing from the spirit or essential attributes thereof and, accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

APPENDIX 1

Factor XI Heavy Chain Domain A3

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 1 | N | ALA | 181 | 1.681 | 6.178 | -12.945 | 1.00 | 0.00 |
| ATOM | 2 | CA | ALA | 181 | 1.610 | 4.951 | -12.171 | 1.00 | 0.00 |
| ATOM | 3 | C | ALA | 181 | 1.733 | 5.177 | -10.659 | 1.00 | 0.00 |
| ATOM | 4 | O | ALA | 181 | 1.441 | 4.262 | -9.891 | 1.00 | 0.00 |
| ATOM | 5 | CB | ALA | 181 | 0.324 | 4.205 | -12.524 | 1.00 | 0.00 |
| ATOM | 6 | H | ALA | 181 | 1.161 | 6.237 | -13.808 | 1.00 | 0.00 |
| ATOM | 7 | N | CYS | 182 | 2.160 | 6.380 | -10.239 | 1.00 | 0.00 |
| ATOM | 8 | CA | CYS | 182 | 2.284 | 6.814 | -8.849 | 1.00 | 0.00 |
| ATOM | 9 | C | CYS | 182 | 1.128 | 6.376 | -7.948 | 1.00 | 0.00 |
| ATOM | 10 | O | CYS | 182 | 1.357 | 5.728 | -6.929 | 1.00 | 0.00 |
| ATOM | 11 | CB | CYS | 182 | 3.649 | 6.433 | -8.269 | 1.00 | 0.00 |
| ATOM | 12 | SG | CYS | 182 | 4.253 | 7.558 | -6.976 | 1.00 | 0.00 |
| ATOM | 13 | LPG1 | CYS | 182 | 4.465 | 8.054 | -7.396 | 1.00 | 0.00 |
| ATOM | 14 | LPG2 | CYS | 182 | 3.924 | 7.273 | -6.461 | 1.00 | 0.00 |
| ATOM | 15 | H | CYS | 182 | 2.386 | 7.073 | -10.938 | 1.00 | 0.00 |
| ATOM | 16 | N | ILE | 183 | -0.120 | 6.711 | -8.296 | 1.00 | 0.00 |
| ATOM | 17 | CA | ILE | 183 | -0.499 | 7.503 | -9.456 | 1.00 | 0.00 |
| ATOM | 18 | C | ILE | 183 | -0.466 | 9.031 | -9.260 | 1.00 | 0.00 |
| ATOM | 19 | O | ILE | 183 | -0.291 | 9.742 | -10.248 | 1.00 | 0.00 |
| ATOM | 20 | CB | ILE | 183 | -1.854 | 7.030 | -9.992 | 1.00 | 0.00 |
| ATOM | 21 | CG1 | ILE | 183 | -1.889 | 5.506 | -10.109 | 1.00 | 0.00 |
| ATOM | 22 | CG2 | ILE | 183 | -2.116 | 7.635 | -11.371 | 1.00 | 0.00 |
| ATOM | 23 | CD1 | ILE | 183 | -3.259 | 5.046 | -10.603 | 1.00 | 0.00 |
| ATOM | 24 | H | ILE | 183 | -0.873 | 6.392 | -7.704 | 1.00 | 0.00 |
| ATOM | 25 | N | ARG | 184 | -0.644 | 9.585 | -8.050 | 1.00 | 0.00 |
| ATOM | 26 | CA | ARG | 184 | -0.723 | 8.870 | -6.792 | 1.00 | 0.00 |
| ATOM | 27 | C | ARG | 184 | -2.132 | 8.417 | -6.434 | 1.00 | 0.00 |
| ATOM | 28 | O | ARG | 184 | -3.117 | 9.048 | -6.817 | 1.00 | 0.00 |
| ATOM | 29 | CB | ARG | 184 | -0.051 | 9.651 | -5.669 | 1.00 | 0.00 |
| ATOM | 30 | CG | ARG | 184 | 0.175 | 8.685 | -4.512 | 1.00 | 0.00 |
| ATOM | 31 | CD | ARG | 184 | 0.890 | 9.372 | -3.360 | 1.00 | 0.00 |
| ATOM | 32 | NE | ARG | 184 | 0.808 | 8.554 | -2.152 | 1.00 | 0.00 |
| ATOM | 33 | CZ | ARG | 184 | 1.865 | 8.157 | -1.421 | 1.00 | 0.00 |
| ATOM | 34 | NH1 | ARG | 184 | 3.114 | 8.438 | -1.824 | 1.00 | 0.00 |
| ATOM | 35 | NH2 | ARG | 184 | 1.662 | 7.503 | -0.276 | 1.00 | 0.00 |
| ATOM | 36 | H | ARG | 184 | -0.663 | 10.593 | -7.991 | 1.00 | 0.00 |
| ATOM | 37 | N | ASP | 185 | -2.180 | 7.311 | -5.683 | 1.00 | 0.00 |
| ATOM | 38 | CA | ASP | 185 | -3.376 | 6.698 | -5.148 | 1.00 | 0.00 |
| ATOM | 39 | C | ASP | 185 | -3.593 | 7.193 | -3.716 | 1.00 | 0.00 |
| ATOM | 40 | O | ASP | 185 | -3.568 | 8.394 | -3.470 | 1.00 | 0.00 |
| ATOM | 41 | CB | ASP | 185 | -4.532 | 6.737 | -6.171 | 1.00 | 0.00 |
| ATOM | 42 | CG | ASP | 185 | -5.894 | 7.245 | -5.702 | 1.00 | 0.00 |
| ATOM | 43 | OD1 | ASP | 185 | -6.609 | 7.828 | -6.544 | 1.00 | 0.00 |
| ATOM | 44 | OD2 | ASP | 185 | -6.216 | 7.010 | -4.528 | 1.00 | 0.00 |
| ATOM | 45 | H | ASP | 185 | -1.305 | 6.927 | -5.356 | 1.00 | 0.00 |
| ATOM | 46 | N | ILE | 186 | -3.750 | 6.259 | -2.774 | 1.00 | 0.00 |
| ATOM | 47 | CA | ILE | 186 | -3.961 | 6.543 | -1.357 | 1.00 | 0.00 |
| ATOM | 48 | C | ILE | 186 | -5.403 | 6.966 | -1.019 | 1.00 | 0.00 |
| ATOM | 49 | O | ILE | 186 | -5.606 | 7.652 | -0.020 | 1.00 | 0.00 |
| ATOM | 50 | CB | ILE | 186 | -3.497 | 5.359 | -0.500 | 1.00 | 0.00 |
| ATOM | 51 | CG1 | ILE | 186 | -3.000 | 5.850 | 0.858 | 1.00 | 0.00 |
| ATOM | 52 | CG2 | ILE | 186 | -2.352 | 4.587 | -1.157 | 1.00 | 0.00 |
| ATOM | 53 | CD1 | ILE | 186 | -4.042 | 5.560 | 1.931 | 1.00 | 0.00 |
| ATOM | 54 | H | ILE | 186 | -3.628 | 5.291 | -3.036 | 1.00 | 0.00 |
| ATOM | 55 | N | PHE | 187 | -6.386 | 6.570 | -1.846 | 1.00 | 0.00 |
| ATOM | 56 | CA | PHE | 187 | -7.802 | 6.935 | -1.730 | 1.00 | 0.00 |
| ATOM | 57 | C | PHE | 187 | -8.686 | 6.355 | -2.852 | 1.00 | 0.00 |
| ATOM | 58 | O | PHE | 187 | -8.790 | 6.910 | -3.942 | 1.00 | 0.00 |
| ATOM | 59 | CB | PHE | 187 | -8.011 | 8.442 | -1.534 | 1.00 | 0.00 |
| ATOM | 60 | CG | PHE | 187 | -7.459 | 9.354 | -2.607 | 1.00 | 0.00 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 61 | CD1 | PHE | 187 | -8.323 | 9.989 | -3.515 | 1.00 | 0.00 |
| ATOM | 62 | CD2 | PHE | 187 | -6.085 | 9.653 | -2.636 | 1.00 | 0.00 |
| ATOM | 63 | CE1 | PHE | 187 | -7.797 | 10.800 | -4.537 | 1.00 | 0.00 |
| ATOM | 64 | CE2 | PHE | 187 | -5.560 | 10.456 | -3.659 | 1.00 | 0.00 |
| ATOM | 65 | CZ | PHE | 187 | -6.409 | 10.986 | -4.645 | 1.00 | 0.00 |
| ATOM | 66 | H | PHE | 187 | -6.121 | 6.029 | -2.655 | 1.00 | 0.00 |
| ATOM | 67 | N | PRO | 188 | -9.356 | 5.235 | -2.578 | 1.00 | 0.00 |
| ATOM | 68 | CA | PRO | 188 | -10.149 | 4.464 | -3.517 | 1.00 | 0.00 |
| ATOM | 69 | C | PRO | 188 | -9.227 | 3.483 | -4.218 | 1.00 | 0.00 |
| ATOM | 70 | O | PRO | 188 | -8.158 | 3.177 | -3.705 | 1.00 | 0.00 |
| ATOM | 71 | CB | PRO | 188 | -11.019 | 3.577 | -2.632 | 1.00 | 0.00 |
| ATOM | 72 | CG | PRO | 188 | -10.088 | 3.265 | -1.464 | 1.00 | 0.00 |
| ATOM | 73 | CD | PRO | 188 | -9.285 | 4.559 | -1.318 | 1.00 | 0.00 |
| ATOM | 74 | N | ASN | 189 | -9.685 | 2.914 | -5.332 | 1.00 | 0.00 |
| ATOM | 75 | CA | ASN | 189 | -9.375 | 1.533 | -5.665 | 1.00 | 0.00 |
| ATOM | 76 | C | ASN | 189 | -10.269 | 0.445 | -5.032 | 1.00 | 0.00 |
| ATOM | 77 | O | ASN | 189 | -11.276 | 0.087 | -5.638 | 1.00 | 0.00 |
| ATOM | 78 | CB | ASN | 189 | -7.901 | 1.246 | -6.021 | 1.00 | 0.00 |
| ATOM | 79 | CG | ASN | 189 | -7.009 | 0.627 | -4.939 | 1.00 | 0.00 |
| ATOM | 80 | OD1 | ASN | 189 | -7.006 | -0.585 | -4.750 | 1.00 | 0.00 |
| ATOM | 81 | ND2 | ASN | 189 | -6.181 | 1.439 | -4.278 | 1.00 | 0.00 |
| ATOM | 82 | H | ASN | 189 | -10.371 | 3.399 | -5.893 | 1.00 | 0.00 |
| ATOM | 83 | N | THR | 190 | -9.867 | -0.095 | -3.866 | 1.00 | 0.00 |
| ATOM | 84 | CA | THR | 190 | -10.287 | -1.371 | -3.261 | 1.00 | 0.00 |
| ATOM | 85 | C | THR | 190 | -11.449 | -2.119 | -3.915 | 1.00 | 0.00 |
| ATOM | 86 | O | THR | 190 | -12.603 | -1.783 | -3.655 | 1.00 | 0.00 |
| ATOM | 87 | CB | THR | 190 | -10.481 | -1.228 | -1.747 | 1.00 | 0.00 |
| ATOM | 88 | OG1 | THR | 190 | -11.148 | -0.023 | -1.436 | 1.00 | 0.00 |
| ATOM | 89 | CG2 | THR | 190 | -9.126 | -1.273 | -1.047 | 1.00 | 0.00 |
| ATOM | 90 | HG1 | THR | 190 | -10.871 | 0.265 | -0.564 | 1.00 | 0.00 |
| ATOM | 91 | H | THR | 190 | -9.112 | 0.371 | -3.388 | 1.00 | 0.00 |
| ATOM | 92 | N | VAL | 191 | -11.204 | -3.148 | -4.746 | 1.00 | 0.00 |
| ATOM | 93 | CA | VAL | 191 | -9.928 | -3.696 | -5.198 | 1.00 | 0.00 |
| ATOM | 94 | C | VAL | 191 | -9.490 | -4.942 | -4.442 | 1.00 | 0.00 |
| ATOM | 95 | O | VAL | 191 | -9.412 | -6.016 | -5.032 | 1.00 | 0.00 |
| ATOM | 96 | CB | VAL | 191 | -8.813 | -2.676 | -5.416 | 1.00 | 0.00 |
| ATOM | 97 | CG1 | VAL | 191 | -7.533 | -3.395 | -5.831 | 1.00 | 0.00 |
| ATOM | 98 | CG2 | VAL | 191 | -9.190 | -1.778 | -6.585 | 1.00 | 0.00 |
| ATOM | 99 | H | VAL | 191 | -12.015 | -3.621 | -5.114 | 1.00 | 0.00 |
| ATOM | 100 | N | PHE | 192 | -9.171 | -4.804 | -3.155 | 1.00 | 0.00 |
| ATOM | 101 | CA | PHE | 192 | -8.740 | -5.946 | -2.376 | 1.00 | 0.00 |
| ATOM | 102 | C | PHE | 192 | -9.781 | -6.336 | -1.338 | 1.00 | 0.00 |
| ATOM | 103 | O | PHE | 192 | -10.434 | -5.484 | -0.739 | 1.00 | 0.00 |
| ATOM | 104 | CB | PHE | 192 | -7.353 | -5.716 | -1.783 | 1.00 | 0.00 |
| ATOM | 105 | CG | PHE | 192 | -6.274 | -5.522 | -2.823 | 1.00 | 0.00 |
| ATOM | 106 | CD1 | PHE | 192 | -5.711 | -4.248 | -3.010 | 1.00 | 0.00 |
| ATOM | 107 | CD2 | PHE | 192 | -5.936 | -6.574 | -3.693 | 1.00 | 0.00 |
| ATOM | 108 | CE1 | PHE | 192 | -4.787 | -4.032 | -4.048 | 1.00 | 0.00 |
| ATOM | 109 | CE2 | PHE | 192 | -5.015 | -6.358 | -4.734 | 1.00 | 0.00 |
| ATOM | 110 | CZ | PHE | 192 | -4.443 | -5.086 | -4.912 | 1.00 | 0.00 |
| ATOM | 111 | H | PHE | 192 | -9.214 | -3.900 | -2.709 | 1.00 | 0.00 |
| ATOM | 112 | N | ALA | 193 | -9.947 | -7.644 | -1.144 | 1.00 | 0.00 |
| ATOM | 113 | CA | ALA | 193 | -9.199 | -8.618 | -1.910 | 1.00 | 0.00 |
| ATOM | 114 | C | ALA | 193 | -10.134 | -9.300 | -2.896 | 1.00 | 0.00 |
| ATOM | 115 | O | ALA | 193 | -10.801 | -10.254 | -2.500 | 1.00 | 0.00 |
| ATOM | 116 | CB | ALA | 193 | -8.568 | -9.633 | -0.959 | 1.00 | 0.00 |
| ATOM | 117 | H | ALA | 193 | -10.636 | -7.979 | -0.485 | 1.00 | 0.00 |
| ATOM | 118 | N | ASP | 194 | -10.163 | -8.811 | -4.150 | 1.00 | 0.00 |
| ATOM | 119 | CA | ASP | 194 | -10.859 | -9.410 | -5.293 | 1.00 | 0.00 |
| ATOM | 120 | C | ASP | 194 | -11.956 | -8.497 | -5.846 | 1.00 | 0.00 |
| ATOM | 121 | O | ASP | 194 | -13.108 | -8.915 | -5.926 | 1.00 | 0.00 |
| ATOM | 122 | CB | ASP | 194 | -11.338 | -10.835 | -4.959 | 1.00 | 0.00 |
| ATOM | 123 | CG | ASP | 194 | -12.128 | -11.621 | -6.002 | 1.00 | 0.00 |
| ATOM | 124 | OD1 | ASP | 194 | -12.127 | -11.216 | -7.186 | 1.00 | 0.00 |
| ATOM | 125 | OD2 | ASP | 194 | -12.723 | -12.634 | -5.578 | 1.00 | 0.00 |
| ATOM | 126 | H | ASP | 194 | -9.618 | -7.981 | -4.343 | 1.00 | 0.00 |
| ATOM | 127 | N | SER | 195 | -11.603 | -7.272 | -6.265 | 1.00 | 0.00 |
| ATOM | 128 | CA | SER | 195 | -12.504 | -6.379 | -6.978 | 1.00 | 0.00 |
| ATOM | 129 | C | SER | 195 | -13.561 | -5.770 | -6.056 | 1.00 | 0.00 |
| ATOM | 130 | O | SER | 195 | -13.527 | -4.575 | -5.771 | 1.00 | 0.00 |
| ATOM | 131 | CB | SER | 195 | -13.122 | -7.119 | -8.170 | 1.00 | 0.00 |
| ATOM | 132 | OG | SER | 195 | -13.982 | -6.283 | -8.908 | 1.00 | 0.00 |
| ATOM | 133 | H | SER | 195 | -10.652 | -6.952 | -6.138 | 1.00 | 0.00 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 134 | N | ASN | 196 | -14.522 | -6.590 | -5.628 | 1.00 | 0.00 |
| ATOM | 135 | CA | ASN | 196 | -15.708 | -6.133 | -4.941 | 1.00 | 0.00 |
| ATOM | 136 | C | ASN | 196 | -15.618 | -6.386 | -3.443 | 1.00 | 0.00 |
| ATOM | 137 | O | ASN | 196 | -15.437 | -7.523 | -3.011 | 1.00 | 0.00 |
| ATOM | 138 | CB | ASN | 196 | -16.934 | -6.814 | -5.544 | 1.00 | 0.00 |
| ATOM | 139 | CG | ASN | 196 | -17.418 | -6.089 | -6.793 | 1.00 | 0.00 |
| ATOM | 140 | OD1 | ASN | 196 | -18.419 | -5.377 | -6.746 | 1.00 | 0.00 |
| ATOM | 141 | ND2 | ASN | 196 | -16.718 | -6.274 | -7.913 | 1.00 | 0.00 |
| ATOM | 142 | H | ASN | 196 | -14.470 | -7.570 | -5.869 | 1.00 | 0.00 |
| ATOM | 143 | N | ILE | 197 | -15.761 | -5.327 | -2.641 | 1.00 | 0.00 |
| ATOM | 144 | CA | ILE | 197 | -15.845 | -3.952 | -3.110 | 1.00 | 0.00 |
| ATOM | 145 | C | ILE | 197 | -15.862 | -3.007 | -1.920 | 1.00 | 0.00 |
| ATOM | 146 | O | ILE | 197 | -16.788 | -3.026 | -1.115 | 1.00 | 0.00 |
| ATOM | 147 | CB | ILE | 197 | -17.038 | -3.724 | -4.045 | 1.00 | 0.00 |
| ATOM | 148 | CG1 | ILE | 197 | -17.129 | -2.251 | -4.446 | 1.00 | 0.00 |
| ATOM | 149 | CG2 | ILE | 197 | -18.352 | -4.166 | -3.405 | 1.00 | 0.00 |
| ATOM | 150 | CD1 | ILE | 197 | -15.829 | -1.795 | -5.104 | 1.00 | 0.00 |
| ATOM | 151 | H | ILE | 197 | -15.755 | -5.476 | -1.642 | 1.00 | 0.00 |
| ATOM | 152 | N | ASP | 198 | -14.814 | -2.194 | -1.800 | 1.00 | 0.00 |
| ATOM | 153 | CA | ASP | 198 | -14.632 | -1.337 | -0.645 | 1.00 | 0.00 |
| ATOM | 154 | C | ASP | 198 | -14.762 | 0.108 | -1.115 | 1.00 | 0.00 |
| ATOM | 155 | O | ASP | 198 | -14.383 | 0.423 | -2.242 | 1.00 | 0.00 |
| ATOM | 156 | CB | ASP | 198 | -13.264 | -1.570 | 0.014 | 1.00 | 0.00 |
| ATOM | 157 | CG | ASP | 198 | -12.774 | -3.021 | 0.138 | 1.00 | 0.00 |
| ATOM | 158 | OD1 | ASP | 198 | -13.450 | -3.939 | -0.370 | 1.00 | 0.00 |
| ATOM | 159 | OD2 | ASP | 198 | -11.696 | -3.183 | 0.743 | 1.00 | 0.00 |
| ATOM | 160 | H | ASP | 198 | -14.064 | -2.241 | -2.475 | 1.00 | 0.00 |
| ATOM | 161 | N | SER | 199 | -15.309 | 1.006 | -0.291 | 1.00 | 0.00 |
| ATOM | 162 | CA | SER | 199 | -15.771 | 0.784 | 1.071 | 1.00 | 0.00 |
| ATOM | 163 | C | SER | 199 | -17.046 | -0.069 | 1.155 | 1.00 | 0.00 |
| ATOM | 164 | O | SER | 199 | -17.331 | -0.630 | 2.211 | 1.00 | 0.00 |
| ATOM | 165 | CB | SER | 199 | -15.988 | 2.177 | 1.674 | 1.00 | 0.00 |
| ATOM | 166 | OG | SER | 199 | -16.662 | 2.154 | 2.911 | 1.00 | 0.00 |
| ATOM | 167 | H | SER | 199 | -15.400 | 1.949 | -0.639 | 1.00 | 0.00 |
| ATOM | 168 | N | VAL | 200 | -17.823 | -0.129 | 0.064 | 1.00 | 0.00 |
| ATOM | 169 | CA | VAL | 200 | -19.237 | -0.477 | 0.055 | 1.00 | 0.00 |
| ATOM | 170 | C | VAL | 200 | -19.695 | -1.741 | 0.790 | 1.00 | 0.00 |
| ATOM | 171 | O | VAL | 200 | -20.743 | -1.696 | 1.431 | 1.00 | 0.00 |
| ATOM | 172 | CB | VAL | 200 | -19.837 | -0.297 | -1.339 | 1.00 | 0.00 |
| ATOM | 173 | CG1 | VAL | 200 | -19.734 | -1.571 | -2.174 | 1.00 | 0.00 |
| ATOM | 174 | CG2 | VAL | 200 | -21.291 | 0.151 | -1.227 | 1.00 | 0.00 |
| ATOM | 175 | H | VAL | 200 | -17.481 | 0.309 | -0.779 | 1.00 | 0.00 |
| ATOM | 176 | N | MET | 201 | -18.958 | -2.856 | 0.706 | 1.00 | 0.00 |
| ATOM | 177 | CA | MET | 201 | -19.349 | -4.080 | 1.389 | 1.00 | 0.00 |
| ATOM | 178 | C | MET | 201 | -19.136 | -3.944 | 2.894 | 1.00 | 0.00 |
| ATOM | 179 | O | MET | 201 | -18.011 | -4.057 | 3.380 | 1.00 | 0.00 |
| ATOM | 180 | CB | MET | 201 | -18.648 | -5.297 | 0.788 | 1.00 | 0.00 |
| ATOM | 181 | CG | MET | 201 | -19.445 | -6.556 | 1.125 | 1.00 | 0.00 |
| ATOM | 182 | SD | MET | 201 | -18.595 | -7.703 | 2.238 | 1.00 | 0.00 |
| ATOM | 183 | CE | MET | 201 | -19.884 | -8.961 | 2.420 | 1.00 | 0.00 |
| ATOM | 184 | LPD1 | MET | 201 | -18.235 | -8.024 | 1.760 | 1.00 | 0.00 |
| ATOM | 185 | LPD2 | MET | 201 | -18.727 | -7.367 | 2.813 | 1.00 | 0.00 |
| ATOM | 186 | H | MET | 201 | -18.108 | -2.863 | 0.159 | 1.00 | 0.00 |
| ATOM | 187 | N | ALA | 202 | -20.238 | -3.653 | 3.600 | 1.00 | 0.00 |
| ATOM | 188 | CA | ALA | 202 | -20.261 | -3.210 | 4.986 | 1.00 | 0.00 |
| ATOM | 189 | C | ALA | 202 | -19.309 | -2.033 | 5.178 | 1.00 | 0.00 |
| ATOM | 190 | O | ALA | 202 | -18.212 | -2.219 | 5.698 | 1.00 | 0.00 |
| ATOM | 191 | CB | ALA | 202 | -19.991 | -4.373 | 5.940 | 1.00 | 0.00 |
| ATOM | 192 | H | ALA | 202 | -21.111 | -3.597 | 3.096 | 1.00 | 0.00 |
| ATOM | 193 | N | PRO | 203 | -19.729 | -0.847 | 4.708 | 1.00 | 0.00 |
| ATOM | 194 | CA | PRO | 203 | -18.926 | 0.342 | 4.483 | 1.00 | 0.00 |
| ATOM | 195 | C | PRO | 203 | -17.819 | 0.600 | 5.497 | 1.00 | 0.00 |
| ATOM | 196 | O | PRO | 203 | -18.061 | 1.141 | 6.573 | 1.00 | 0.00 |
| ATOM | 197 | CB | PRO | 203 | -19.896 | 1.509 | 4.335 | 1.00 | 0.00 |
| ATOM | 198 | CG | PRO | 203 | -21.239 | 0.864 | 3.986 | 1.00 | 0.00 |
| ATOM | 199 | CD | PRO | 203 | -21.084 | -0.635 | 4.245 | 1.00 | 0.00 |
| ATOM | 200 | N | ASP | 204 | -16.596 | 0.214 | 5.124 | 1.00 | 0.00 |
| ATOM | 201 | CA | ASP | 204 | -15.427 | 0.422 | 5.951 | 1.00 | 0.00 |
| ATOM | 202 | C | ASP | 204 | -14.546 | 1.506 | 5.349 | 1.00 | 0.00 |
| ATOM | 203 | O | ASP | 204 | -13.969 | 1.323 | 4.277 | 1.00 | 0.00 |
| ATOM | 204 | CB | ASP | 204 | -14.653 | -0.887 | 6.118 | 1.00 | 0.00 |
| ATOM | 205 | CG | ASP | 204 | -15.284 | -1.841 | 7.132 | 1.00 | 0.00 |
| ATOM | 206 | OD1 | ASP | 204 | -16.337 | -1.478 | 7.700 | 1.00 | 0.00 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 207 | OD2 | ASP | 204 | -14.690 | -2.922 | 7.321 | 1.00 | 0.00 |
| ATOM | 208 | H | ASP | 204 | -16.464 | -0.214 | 4.218 | 1.00 | 0.00 |
| ATOM | 209 | N | ALA | 205 | -14.419 | 2.620 | 6.076 | 1.00 | 0.00 |
| ATOM | 210 | CA | ALA | 205 | -13.401 | 3.615 | 5.807 | 1.00 | 0.00 |
| ATOM | 211 | C | ALA | 205 | -12.030 | 3.011 | 6.068 | 1.00 | 0.00 |
| ATOM | 212 | O | ALA | 205 | -11.858 | 2.242 | 7.011 | 1.00 | 0.00 |
| ATOM | 213 | CB | ALA | 205 | -13.637 | 4.865 | 6.650 | 1.00 | 0.00 |
| ATOM | 214 | H | ALA | 205 | -14.941 | 2.711 | 6.934 | 1.00 | 0.00 |
| ATOM | 215 | N | PHE | 206 | -11.050 | 3.316 | 5.220 | 1.00 | 0.00 |
| ATOM | 216 | CA | PHE | 206 | -11.085 | 4.394 | 4.245 | 1.00 | 0.00 |
| ATOM | 217 | C | PHE | 206 | -9.741 | 4.428 | 3.540 | 1.00 | 0.00 |
| ATOM | 218 | O | PHE | 206 | -8.905 | 3.560 | 3.789 | 1.00 | 0.00 |
| ATOM | 219 | CB | PHE | 206 | -12.229 | 4.239 | 3.241 | 1.00 | 0.00 |
| ATOM | 220 | CG | PHE | 206 | -13.158 | 5.434 | 3.197 | 1.00 | 0.00 |
| ATOM | 221 | CD1 | PHE | 206 | -12.674 | 6.698 | 2.813 | 1.00 | 0.00 |
| ATOM | 222 | CD2 | PHE | 206 | -14.491 | 5.297 | 3.622 | 1.00 | 0.00 |
| ATOM | 223 | CE1 | PHE | 206 | -13.523 | 7.818 | 2.850 | 1.00 | 0.00 |
| ATOM | 224 | CE2 | PHE | 206 | -15.322 | 6.425 | 3.715 | 1.00 | 0.00 |
| ATOM | 225 | CZ | PHE | 206 | -14.842 | 7.685 | 3.318 | 1.00 | 0.00 |
| ATOM | 226 | H | PHE | 206 | -10.166 | 2.839 | 5.332 | 1.00 | 0.00 |
| ATOM | 227 | N | VAL | 207 | -9.550 | 5.401 | 2.638 | 1.00 | 0.00 |
| ATOM | 228 | CA | VAL | 207 | -8.374 | 5.477 | 1.781 | 1.00 | 0.00 |
| ATOM | 229 | C | VAL | 207 | -8.103 | 4.109 | 1.155 | 1.00 | 0.00 |
| ATOM | 230 | O | VAL | 207 | -9.021 | 3.301 | 1.023 | 1.00 | 0.00 |
| ATOM | 231 | CB | VAL | 207 | -7.158 | 6.088 | 2.489 | 1.00 | 0.00 |
| ATOM | 232 | CG1 | VAL | 207 | -7.405 | 7.513 | 2.979 | 1.00 | 0.00 |
| ATOM | 233 | CG2 | VAL | 207 | -6.665 | 5.225 | 3.639 | 1.00 | 0.00 |
| ATOM | 234 | H | VAL | 207 | -10.322 | 6.012 | 2.413 | 1.00 | 0.00 |
| ATOM | 235 | N | CYS | 208 | -6.864 | 3.814 | 0.770 | 1.00 | 0.00 |
| ATOM | 236 | CA | CYS | 208 | -6.649 | 2.584 | 0.026 | 1.00 | 0.00 |
| ATOM | 237 | C | CYS | 208 | -6.559 | 1.350 | 0.927 | 1.00 | 0.00 |
| ATOM | 238 | O | CYS | 208 | -6.523 | 0.225 | 0.433 | 1.00 | 0.00 |
| ATOM | 239 | CB | CYS | 208 | -5.532 | 2.742 | -1.006 | 1.00 | 0.00 |
| ATOM | 240 | SG | CYS | 208 | -3.967 | 1.906 | -0.650 | 1.00 | 0.00 |
| ATOM | 241 | LPG1 | CYS | 208 | -4.129 | 1.674 | -0.056 | 1.00 | 0.00 |
| ATOM | 242 | LPG2 | CYS | 208 | -4.129 | 1.674 | -0.056 | 1.00 | 0.00 |
| ATOM | 243 | H | CYS | 208 | -6.078 | 4.353 | 1.102 | 1.00 | 0.00 |
| ATOM | 244 | N | GLY | 209 | -6.538 | 1.573 | 2.246 | 1.00 | 0.00 |
| ATOM | 245 | CA | GLY | 209 | -6.384 | 0.555 | 3.258 | 1.00 | 0.00 |
| ATOM | 246 | C | GLY | 209 | -5.937 | 1.246 | 4.541 | 1.00 | 0.00 |
| ATOM | 247 | O | GLY | 209 | -4.826 | 1.007 | 5.001 | 1.00 | 0.00 |
| ATOM | 248 | H | GLY | 209 | -6.623 | 2.521 | 2.582 | 1.00 | 0.00 |
| ATOM | 249 | N | ARG | 210 | -6.815 | 2.102 | 5.085 | 1.00 | 0.00 |
| ATOM | 250 | CA | ARG | 210 | -6.668 | 2.886 | 6.312 | 1.00 | 0.00 |
| ATOM | 251 | C | ARG | 210 | -6.094 | 2.114 | 7.492 | 1.00 | 0.00 |
| ATOM | 252 | O | ARG | 210 | -4.879 | 1.982 | 7.622 | 1.00 | 0.00 |
| ATOM | 253 | CB | ARG | 210 | -5.956 | 4.221 | 6.092 | 1.00 | 0.00 |
| ATOM | 254 | CG | ARG | 210 | -6.442 | 5.261 | 7.107 | 1.00 | 0.00 |
| ATOM | 255 | CD | ARG | 210 | -6.055 | 6.676 | 6.667 | 1.00 | 0.00 |
| ATOM | 256 | NE | ARG | 210 | -6.500 | 7.693 | 7.629 | 1.00 | 0.00 |
| ATOM | 257 | CZ | ARG | 210 | -5.956 | 8.919 | 7.755 | 1.00 | 0.00 |
| ATOM | 258 | NH1 | ARG | 210 | -5.029 | 9.347 | 6.891 | 1.00 | 0.00 |
| ATOM | 259 | NH2 | ARG | 210 | -6.324 | 9.713 | 8.773 | 1.00 | 0.00 |
| ATOM | 260 | H | ARG | 210 | -7.695 | 2.209 | 4.599 | 1.00 | 0.00 |
| ATOM | 261 | N | ILE | 211 | -6.966 | 1.624 | 8.376 | 1.00 | 0.00 |
| ATOM | 262 | CA | ILE | 211 | -8.405 | 1.782 | 8.256 | 1.00 | 0.00 |
| ATOM | 263 | C | ILE | 211 | -8.976 | 0.651 | 7.404 | 1.00 | 0.00 |
| ATOM | 264 | O | ILE | 211 | -9.263 | 0.858 | 6.226 | 1.00 | 0.00 |
| ATOM | 265 | CB | ILE | 211 | -9.017 | 1.850 | 9.658 | 1.00 | 0.00 |
| ATOM | 266 | CG1 | ILE | 211 | -10.542 | 1.855 | 9.601 | 1.00 | 0.00 |
| ATOM | 267 | CG2 | ILE | 211 | -8.529 | 3.115 | 10.362 | 1.00 | 0.00 |
| ATOM | 268 | CD1 | ILE | 211 | -11.120 | 1.893 | 11.013 | 1.00 | 0.00 |
| ATOM | 269 | H | ILE | 211 | -6.612 | 1.115 | 9.172 | 1.00 | 0.00 |
| ATOM | 270 | N | CYS | 212 | -9.086 | -0.548 | 7.996 | 1.00 | 0.00 |
| ATOM | 271 | CA | CYS | 212 | -9.376 | -1.812 | 7.326 | 1.00 | 0.00 |
| ATOM | 272 | C | CYS | 212 | -10.804 | -1.939 | 6.782 | 1.00 | 0.00 |
| ATOM | 273 | O | CYS | 212 | -11.363 | -0.976 | 6.262 | 1.00 | 0.00 |
| ATOM | 274 | CB | CYS | 212 | -8.287 | -2.251 | 6.336 | 1.00 | 0.00 |
| ATOM | 275 | SG | CYS | 212 | -6.673 | -1.617 | 6.355 | 1.00 | 0.00 |
| ATOM | 276 | LPG1 | CYS | 212 | -6.913 | -0.775 | 6.391 | 1.00 | 0.00 |
| ATOM | 277 | LPG2 | CYS | 212 | -6.913 | -0.775 | 6.391 | 1.00 | 0.00 |
| ATOM | 278 | H | CYS | 212 | -8.844 | -0.607 | 8.974 | 1.00 | 0.00 |
| ATOM | 279 | N | THR | 213 | -11.431 | -3.119 | 6.899 | 1.00 | 0.00 |

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|---|---|---|---|---|---|---|---|---|---|
| ATOM | 280 | CA | THR | 213 | -10.891 | -4.347 | 7.466 | 1.00 | 0.00 |
| ATOM | 281 | C | THR | 213 | -12.044 | -5.339 | 7.666 | 1.00 | 0.00 |
| ATOM | 282 | O | THR | 213 | -12.626 | -5.392 | 8.747 | 1.00 | 0.00 |
| ATOM | 283 | CB | THR | 213 | -10.107 | -4.066 | 8.760 | 1.00 | 0.00 |
| ATOM | 284 | OG1 | THR | 213 | -9.544 | -5.238 | 9.308 | 1.00 | 0.00 |
| ATOM | 285 | CG2 | THR | 213 | -10.924 | -3.322 | 9.816 | 1.00 | 0.00 |
| ATOM | 286 | HG1 | THR | 213 | -9.132 | -5.011 | 10.146 | 1.00 | 0.00 |
| ATOM | 287 | H | THR | 213 | -12.376 | -3.175 | 6.548 | 1.00 | 0.00 |
| ATOM | 288 | N | HIS | 214 | -12.411 | -6.130 | 6.645 | 1.00 | 0.00 |
| ATOM | 289 | CA | HIS | 214 | -11.783 | -6.232 | 5.332 | 1.00 | 0.00 |
| ATOM | 290 | C | HIS | 214 | -10.343 | -6.746 | 5.358 | 1.00 | 0.00 |
| ATOM | 291 | O | HIS | 214 | -9.759 | -6.923 | 6.427 | 1.00 | 0.00 |
| ATOM | 292 | CB | HIS | 214 | -12.031 | -5.004 | 4.457 | 1.00 | 0.00 |
| ATOM | 293 | CG | HIS | 214 | -12.807 | -5.327 | 3.202 | 1.00 | 0.00 |
| ATOM | 294 | ND1 | HIS | 214 | -12.298 | -5.983 | 2.106 | 1.00 | 0.00 |
| ATOM | 295 | CD2 | HIS | 214 | -14.160 | -5.183 | 3.051 | 1.00 | 0.00 |
| ATOM | 296 | CE1 | HIS | 214 | -13.341 | -6.228 | 1.285 | 1.00 | 0.00 |
| ATOM | 297 | NE2 | HIS | 214 | -14.476 | -5.746 | 1.809 | 1.00 | 0.00 |
| ATOM | 298 | H | HIS | 214 | -13.191 | -6.751 | 6.805 | 1.00 | 0.00 |
| ATOM | 299 | N | HIS | 215 | -9.779 | -7.034 | 4.179 | 1.00 | 0.00 |
| ATOM | 300 | CA | HIS | 215 | -8.493 | -7.705 | 4.102 | 1.00 | 0.00 |
| ATOM | 301 | C | HIS | 215 | -7.322 | -6.855 | 4.584 | 1.00 | 0.00 |
| ATOM | 302 | O | HIS | 215 | -7.318 | -5.639 | 4.397 | 1.00 | 0.00 |
| ATOM | 303 | CB | HIS | 215 | -8.281 | -8.388 | 2.754 | 1.00 | 0.00 |
| ATOM | 304 | CG | HIS | 215 | -8.442 | -9.882 | 2.858 | 1.00 | 0.00 |
| ATOM | 305 | ND1 | HIS | 215 | -7.927 | -10.813 | 1.986 | 1.00 | 0.00 |
| ATOM | 306 | CD2 | HIS | 215 | -9.008 | -10.551 | 3.911 | 1.00 | 0.00 |
| ATOM | 307 | CE1 | HIS | 215 | -8.191 | -12.034 | 2.484 | 1.00 | 0.00 |
| ATOM | 308 | NE2 | HIS | 215 | -8.847 | -11.916 | 3.650 | 1.00 | 0.00 |
| ATOM | 309 | HD1 | HIS | 215 | -7.427 | -10.617 | 1.132 | 1.00 | 0.00 |
| ATOM | 310 | H | HIS | 215 | -10.287 | -6.869 | 3.322 | 1.00 | 0.00 |
| ATOM | 311 | N | PRO | 216 | -6.370 | -7.505 | 5.266 | 1.00 | 0.00 |
| ATOM | 312 | CA | PRO | 216 | -5.386 | -6.857 | 6.114 | 1.00 | 0.00 |
| ATOM | 313 | C | PRO | 216 | -4.201 | -6.246 | 5.364 | 1.00 | 0.00 |
| ATOM | 314 | O | PRO | 216 | -3.053 | -6.618 | 5.600 | 1.00 | 0.00 |
| ATOM | 315 | CB | PRO | 216 | -4.934 | -7.895 | 7.142 | 1.00 | 0.00 |
| ATOM | 316 | CG | PRO | 216 | -5.591 | -9.218 | 6.747 | 1.00 | 0.00 |
| ATOM | 317 | CD | PRO | 216 | -6.440 | -8.931 | 5.512 | 1.00 | 0.00 |
| ATOM | 318 | N | GLY | 217 | -4.478 | -5.253 | 4.515 | 1.00 | 0.00 |
| ATOM | 319 | CA | GLY | 217 | -3.469 | -4.342 | 4.013 | 1.00 | 0.00 |
| ATOM | 320 | C | GLY | 217 | -3.693 | -2.993 | 4.682 | 1.00 | 0.00 |
| ATOM | 321 | O | GLY | 217 | -4.251 | -2.082 | 4.072 | 1.00 | 0.00 |
| ATOM | 322 | H | GLY | 217 | -5.444 | -5.019 | 4.336 | 1.00 | 0.00 |
| ATOM | 323 | N | CYS | 218 | -3.297 | -2.887 | 5.954 | 1.00 | 0.00 |
| ATOM | 324 | CA | CYS | 218 | -3.632 | -1.738 | 6.770 | 1.00 | 0.00 |
| ATOM | 325 | C | CYS | 218 | -2.423 | -0.837 | 6.986 | 1.00 | 0.00 |
| ATOM | 326 | O | CYS | 218 | -1.573 | -1.116 | 7.830 | 1.00 | 0.00 |
| ATOM | 327 | CB | CYS | 218 | -4.308 | -2.206 | 8.058 | 1.00 | 0.00 |
| ATOM | 328 | SG | CYS | 218 | -5.957 | -1.493 | 8.271 | 1.00 | 0.00 |
| ATOM | 329 | LPG1 | CYS | 218 | -5.764 | -0.855 | 8.315 | 1.00 | 0.00 |
| ATOM | 330 | LPG2 | CYS | 218 | -6.271 | -2.082 | 8.448 | 1.00 | 0.00 |
| ATOM | 331 | H | CYS | 218 | -2.835 | -3.667 | 6.401 | 1.00 | 0.00 |
| ATOM | 332 | N | LEU | 219 | -2.341 | 0.235 | 6.191 | 1.00 | 0.00 |
| ATOM | 333 | CA | LEU | 219 | -1.176 | 1.102 | 6.159 | 1.00 | 0.00 |
| ATOM | 334 | C | LEU | 219 | -1.561 | 2.570 | 6.260 | 1.00 | 0.00 |
| ATOM | 335 | O | LEU | 219 | -1.534 | 3.316 | 5.282 | 1.00 | 0.00 |
| ATOM | 336 | CB | LEU | 219 | -0.280 | 0.795 | 4.959 | 1.00 | 0.00 |
| ATOM | 337 | CG | LEU | 219 | -1.073 | 0.663 | 3.661 | 1.00 | 0.00 |
| ATOM | 338 | CD1 | LEU | 219 | -0.315 | 1.376 | 2.546 | 1.00 | 0.00 |
| ATOM | 339 | CD2 | LEU | 219 | -1.201 | -0.817 | 3.311 | 1.00 | 0.00 |
| ATOM | 340 | H | LEU | 219 | -3.099 | 0.434 | 5.552 | 1.00 | 0.00 |
| ATOM | 341 | N | PHE | 220 | -1.910 | 2.970 | 7.480 | 1.00 | 0.00 |
| ATOM | 342 | CA | PHE | 220 | -2.361 | 4.301 | 7.790 | 1.00 | 0.00 |
| ATOM | 343 | C | PHE | 220 | -1.193 | 5.293 | 7.873 | 1.00 | 0.00 |
| ATOM | 344 | O | PHE | 220 | -0.508 | 5.363 | 8.893 | 1.00 | 0.00 |
| ATOM | 345 | CB | PHE | 220 | -3.141 | 4.184 | 9.094 | 1.00 | 0.00 |
| ATOM | 346 | CG | PHE | 220 | -4.114 | 5.295 | 9.331 | 1.00 | 0.00 |
| ATOM | 347 | CD1 | PHE | 220 | -5.252 | 5.059 | 10.129 | 1.00 | 0.00 |
| ATOM | 348 | CD2 | PHE | 220 | -3.661 | 6.612 | 9.141 | 1.00 | 0.00 |
| ATOM | 349 | CE1 | PHE | 220 | -5.906 | 6.138 | 10.745 | 1.00 | 0.00 |
| ATOM | 350 | CE2 | PHE | 220 | -4.191 | 7.650 | 9.901 | 1.00 | 0.00 |
| ATOM | 351 | CZ | PHE | 220 | -5.335 | 7.418 | 10.703 | 1.00 | 0.00 |
| ATOM | 352 | H | PHE | 220 | -1.949 | 2.287 | 8.223 | 1.00 | 0.00 |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 353 | N | PHE | 221 | -0.984 | 6.084 | 6.811 | 1.00 | 0.00 |
| ATOM | 354 | CA | PHE | 221 | -0.011 | 7.166 | 6.841 | 1.00 | 0.00 |
| ATOM | 355 | C | PHE | 221 | -0.485 | 8.407 | 6.093 | 1.00 | 0.00 |
| ATOM | 356 | O | PHE | 221 | -0.778 | 9.419 | 6.728 | 1.00 | 0.00 |
| ATOM | 357 | CB | PHE | 221 | 1.377 | 6.703 | 6.405 | 1.00 | 0.00 |
| ATOM | 358 | CG | PHE | 221 | 2.496 | 7.480 | 7.066 | 1.00 | 0.00 |
| ATOM | 359 | CD1 | PHE | 221 | 2.567 | 7.536 | 8.469 | 1.00 | 0.00 |
| ATOM | 360 | CD2 | PHE | 221 | 3.407 | 8.213 | 6.286 | 1.00 | 0.00 |
| ATOM | 361 | CE1 | PHE | 221 | 3.563 | 8.307 | 9.093 | 1.00 | 0.00 |
| ATOM | 362 | CE2 | PHE | 221 | 4.408 | 8.979 | 6.911 | 1.00 | 0.00 |
| ATOM | 363 | CZ | PHE | 221 | 4.486 | 9.026 | 8.314 | 1.00 | 0.00 |
| ATOM | 364 | H | PHE | 221 | -1.563 | 5.985 | 5.989 | 1.00 | 0.00 |
| ATOM | 365 | N | THR | 222 | -0.554 | 8.339 | 4.757 | 1.00 | 0.00 |
| ATOM | 366 | CA | THR | 222 | -0.994 | 9.463 | 3.945 | 1.00 | 0.00 |
| ATOM | 367 | C | THR | 222 | -0.700 | 9.333 | 2.457 | 1.00 | 0.00 |
| ATOM | 368 | O | THR | 222 | -1.540 | 9.019 | 1.615 | 1.00 | 0.00 |
| ATOM | 369 | CB | THR | 222 | -2.375 | 9.984 | 4.304 | 1.00 | 0.00 |
| ATOM | 370 | OG1 | THR | 222 | -3.297 | 8.934 | 4.164 | 1.00 | 0.00 |
| ATOM | 371 | CG2 | THR | 222 | -2.740 | 11.154 | 3.389 | 1.00 | 0.00 |
| ATOM | 372 | HG1 | THR | 222 | -4.159 | 9.317 | 4.001 | 1.00 | 0.00 |
| ATOM | 373 | H | THR | 222 | -0.240 | 7.504 | 4.283 | 1.00 | 0.00 |
| ATOM | 374 | N | PHE | 223 | 0.556 | 9.672 | 2.228 | 1.00 | 0.00 |
| ATOM | 375 | CA | PHE | 223 | 1.299 | 9.979 | 1.030 | 1.00 | 0.00 |
| ATOM | 376 | C | PHE | 223 | 0.791 | 10.929 | -0.059 | 1.00 | 0.00 |
| ATOM | 377 | O | PHE | 223 | -0.352 | 11.385 | -0.078 | 1.00 | 0.00 |
| ATOM | 378 | CB | PHE | 223 | 2.587 | 10.531 | 1.570 | 1.00 | 0.00 |
| ATOM | 379 | CG | PHE | 223 | 3.748 | 9.665 | 1.232 | 1.00 | 0.00 |
| ATOM | 380 | CD1 | PHE | 223 | 4.800 | 10.422 | 0.720 | 1.00 | 0.00 |
| ATOM | 381 | CD2 | PHE | 223 | 4.060 | 8.678 | 2.189 | 1.00 | 0.00 |
| ATOM | 382 | CE1 | PHE | 223 | 5.803 | 10.798 | 1.626 | 1.00 | 0.00 |
| ATOM | 383 | CE2 | PHE | 223 | 5.222 | 8.850 | 2.960 | 1.00 | 0.00 |
| ATOM | 384 | CZ | PHE | 223 | 5.983 | 10.021 | 2.787 | 1.00 | 0.00 |
| ATOM | 385 | H | PHE | 223 | 1.131 | 9.627 | 3.057 | 1.00 | 0.00 |
| ATOM | 386 | N | PHE | 224 | 1.736 | 11.194 | -0.977 | 1.00 | 0.00 |
| ATOM | 387 | CA | PHE | 224 | 1.677 | 12.196 | -2.022 | 1.00 | 0.00 |
| ATOM | 388 | C | PHE | 224 | 2.947 | 12.157 | -2.894 | 1.00 | 0.00 |
| ATOM | 389 | O | PHE | 224 | 3.920 | 11.472 | -2.577 | 1.00 | 0.00 |
| ATOM | 390 | CB | PHE | 224 | 1.520 | 13.545 | -1.328 | 1.00 | 0.00 |
| ATOM | 391 | CG | PHE | 224 | 0.980 | 14.652 | -2.194 | 1.00 | 0.00 |
| ATOM | 392 | CD1 | PHE | 224 | -0.406 | 14.859 | -2.296 | 1.00 | 0.00 |
| ATOM | 393 | CD2 | PHE | 224 | 1.871 | 15.489 | -2.885 | 1.00 | 0.00 |
| ATOM | 394 | CE1 | PHE | 224 | -0.898 | 15.878 | -3.130 | 1.00 | 0.00 |
| ATOM | 395 | CE2 | PHE | 224 | 1.378 | 16.445 | -3.787 | 1.00 | 0.00 |
| ATOM | 396 | CZ | PHE | 224 | -0.008 | 16.646 | -3.903 | 1.00 | 0.00 |
| ATOM | 397 | H | PHE | 224 | 2.618 | 10.709 | -0.888 | 1.00 | 0.00 |
| ATOM | 398 | N | SER | 225 | 2.929 | 12.908 | -4.00 | 1.00 | 0.00 |
| ATOM | 399 | CA | SER | 225 | 4.034 | 13.048 | -4.939 | 1.00 | 0.00 |
| ATOM | 400 | C | SER | 225 | 3.890 | 12.022 | -6.069 | 1.00 | 0.00 |
| ATOM | 401 | O | SER | 225 | 3.334 | 10.942 | -5.871 | 1.00 | 0.00 |
| ATOM | 402 | CB | SER | 225 | 4.036 | 14.498 | -5.449 | 1.00 | 0.00 |
| ATOM | 403 | OG | SER | 225 | 5.185 | 14.821 | -6.208 | 1.00 | 0.00 |
| ATOM | 404 | H | SER | 225 | 2.102 | 13.450 | -4.204 | 1.00 | 0.00 |
| ATOM | 405 | N | GLN | 226 | 4.395 | 12.365 | -7.258 | 1.00 | 0.00 |
| ATOM | 406 | CA | GLN | 226 | 4.304 | 11.559 | -8.461 | 1.00 | 0.00 |
| ATOM | 407 | C | GLN | 226 | 5.664 | 10.983 | -8.858 | 1.00 | 0.00 |
| ATOM | 408 | O | GLN | 226 | 6.674 | 11.245 | -8.206 | 1.00 | 0.00 |
| ATOM | 409 | CB | GLN | 226 | 3.732 | 12.428 | -9.583 | 1.00 | 0.00 |
| ATOM | 410 | CG | GLN | 226 | 4.579 | 13.689 | -9.762 | 1.00 | 0.00 |
| ATOM | 411 | CD | GLN | 226 | 3.722 | 14.880 | -10.166 | 1.00 | 0.00 |
| ATOM | 412 | OE1 | GLN | 226 | 3.298 | 15.660 | -9.315 | 1.00 | 0.00 |
| ATOM | 413 | NE2 | GLN | 226 | 3.471 | 15.019 | -11.469 | 1.00 | 0.00 |
| ATOM | 414 | H | GLN | 226 | 4.835 | 13.270 | -7.347 | 1.00 | 0.00 |
| ATOM | 415 | N | GLU | 227 | 5.671 | 10.210 | -9.953 | 1.00 | 0.00 |
| ATOM | 416 | CA | GLU | 227 | 6.859 | 9.634 | -10.569 | 1.00 | 0.00 |
| ATOM | 417 | C | GLU | 227 | 7.312 | 8.327 | -9.906 | 1.00 | 0.00 |
| ATOM | 418 | O | GLU | 227 | 7.740 | 8.351 | -8.754 | 1.00 | 0.00 |
| ATOM | 419 | CB | GLU | 227 | 7.982 | 10.672 | -10.687 | 1.00 | 0.00 |
| ATOM | 420 | CG | GLU | 227 | 8.413 | 10.865 | -12.142 | 1.00 | 0.00 |
| ATOM | 421 | CD | GLU | 227 | 9.525 | 11.904 | -12.302 | 1.00 | 0.00 |
| ATOM | 422 | OE1 | GLU | 227 | 9.931 | 12.486 | -11.272 | 1.00 | 0.00 |
| ATOM | 423 | OE2 | GLU | 227 | 9.949 | 12.098 | -13.461 | 1.00 | 0.00 |
| ATOM | 424 | H | GLU | 227 | 4.793 | 10.061 | -10.428 | 1.00 | 0.00 |
| ATOM | 425 | N | TRP | 228 | 7.228 | 7.216 | -10.673 | 1.00 | 0.00 |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 426 | CA | TRP | 228 | 8.086 | 6.014 | -10.705 | 1.00 | 0.00 |
| ATOM | 427 | C | TRP | 228 | 7.373 | 4.655 | -10.953 | 1.00 | 0.00 |
| ATOM | 428 | O | TRP | 228 | 6.137 | 4.643 | -11.001 | 1.00 | 0.00 |
| ATOM | 429 | CB | TRP | 228 | 9.320 | 6.270 | -11.584 | 1.00 | 0.00 |
| ATOM | 430 | CG | TRP | 228 | 9.072 | 6.774 | -12.965 | 1.00 | 0.00 |
| ATOM | 431 | CD1 | TRP | 228 | 8.103 | 7.661 | -13.305 | 1.00 | 0.00 |
| ATOM | 432 | CD2 | TRP | 228 | 9.815 | 6.503 | -14.187 | 1.00 | 0.00 |
| ATOM | 433 | NE1 | TRP | 228 | 8.192 | 7.949 | -14.643 | 1.00 | 0.00 |
| ATOM | 434 | CE2 | TRP | 228 | 9.238 | 7.282 | -15.235 | 1.00 | 0.00 |
| ATOM | 435 | CE3 | TRP | 228 | 10.925 | 5.702 | -14.521 | 1.00 | 0.00 |
| ATOM | 436 | CZ2 | TRP | 228 | 9.741 | 7.269 | -16.542 | 1.00 | 0.00 |
| ATOM | 437 | CZ3 | TRP | 228 | 11.434 | 5.679 | -15.832 | 1.00 | 0.00 |
| ATOM | 438 | CH2 | TRP | 228 | 10.847 | 6.467 | -16.841 | 1.00 | 0.00 |
| ATOM | 439 | N | PRO | 229 | 8.111 | 3.502 | -11.044 | 1.00 | 0.00 |
| ATOM | 440 | CA | PRO | 229 | 7.678 | 2.225 | -10.448 | 1.00 | 0.00 |
| ATOM | 441 | C | PRO | 229 | 8.021 | 0.815 | -11.000 | 1.00 | 0.00 |
| ATOM | 442 | O | PRO | 229 | 7.536 | -0.157 | -10.413 | 1.00 | 0.00 |
| ATOM | 443 | CB | PRO | 229 | 8.625 | 2.128 | -9.275 | 1.00 | 0.00 |
| ATOM | 444 | CG | PRO | 229 | 9.964 | 2.649 | -9.813 | 1.00 | 0.00 |
| ATOM | 445 | CD | PRO | 229 | 9.554 | 3.589 | -10.947 | 1.00 | 0.00 |
| ATOM | 446 | N | LYS | 230 | 9.050 | 0.657 | -11.843 | 1.00 | 0.00 |
| ATOM | 447 | CA | LYS | 230 | 10.279 | -0.025 | -11.393 | 1.00 | 0.00 |
| ATOM | 448 | C | LYS | 230 | 11.502 | 0.890 | -11.560 | 1.00 | 0.00 |
| ATOM | 449 | O | LYS | 230 | 11.469 | 1.845 | -12.310 | 1.00 | 0.00 |
| ATOM | 450 | CB | LYS | 230 | 10.510 | -1.323 | -12.161 | 1.00 | 0.00 |
| ATOM | 451 | CG | LYS | 230 | 9.426 | -2.317 | -11.769 | 1.00 | 0.00 |
| ATOM | 452 | CD | LYS | 230 | 9.711 | -3.653 | -12.442 | 1.00 | 0.00 |
| ATOM | 453 | CE | LYS | 230 | 9.307 | -3.566 | -13.909 | 1.00 | 0.00 |
| ATOM | 454 | NZ | LYS | 230 | 9.583 | -4.831 | -14.605 | 1.00 | 0.00 |
| ATOM | 455 | H | LYS | 230 | 9.184 | 1.324 | -12.586 | 1.00 | 0.00 |
| ATOM | 456 | N | GLU | 231 | 12.592 | 0.637 | -10.807 | 1.00 | 0.00 |
| ATOM | 457 | CA | GLU | 231 | 12.722 | -0.424 | -9.848 | 1.00 | 0.00 |
| ATOM | 458 | C | GLU | 231 | 12.257 | 0.053 | -8.480 | 1.00 | 0.00 |
| ATOM | 459 | O | GLU | 231 | 11.349 | -0.545 | -7.906 | 1.00 | 0.00 |
| ATOM | 460 | CB | GLU | 231 | 14.203 | -0.764 | -9.792 | 1.00 | 0.00 |
| ATOM | 461 | CG | GLU | 231 | 14.336 | -2.243 | -9.506 | 1.00 | 0.00 |
| ATOM | 462 | CD | GLU | 231 | 14.162 | -2.548 | -8.038 | 1.00 | 0.00 |
| ATOM | 463 | OE1 | GLU | 231 | 14.048 | -1.611 | -7.215 | 1.00 | 0.00 |
| ATOM | 464 | OE2 | GLU | 231 | 14.192 | -3.765 | -7.766 | 1.00 | 0.00 |
| ATOM | 465 | H | GLU | 231 | 13.410 | 1.212 | -10.927 | 1.00 | 0.00 |
| ATOM | 466 | N | SER | 232 | 12.957 | 1.064 | -7.942 | 1.00 | 0.00 |
| ATOM | 467 | CA | SER | 232 | 12.908 | 1.459 | -6.541 | 1.00 | 0.00 |
| ATOM | 468 | C | SER | 232 | 11.648 | 2.237 | -6.206 | 1.00 | 0.00 |
| ATOM | 469 | O | SER | 232 | 11.737 | 3.367 | -5.777 | 1.00 | 0.00 |
| ATOM | 470 | CB | SER | 232 | 14.167 | 2.218 | -6.095 | 1.00 | 0.00 |
| ATOM | 471 | OG | SER | 232 | 15.017 | 2.584 | -7.161 | 1.00 | 0.00 |
| ATOM | 472 | N | GLN | 233 | 10.492 | 1.580 | -6.381 | 1.00 | 0.00 |
| ATOM | 473 | CA | GLN | 233 | 9.174 | 2.030 | -5.955 | 1.00 | 0.00 |
| ATOM | 474 | C | GLN | 233 | 8.279 | 0.824 | -5.701 | 1.00 | 0.00 |
| ATOM | 475 | O | GLN | 233 | 7.794 | 0.675 | -4.583 | 1.00 | 0.00 |
| ATOM | 476 | CB | GLN | 233 | 8.559 | 3.081 | -6.882 | 1.00 | 0.00 |
| ATOM | 477 | CG | GLN | 233 | 9.741 | 3.929 | -7.344 | 1.00 | 0.00 |
| ATOM | 478 | CD | GLN | 233 | 9.442 | 5.152 | -8.153 | 1.00 | 0.00 |
| ATOM | 479 | OE1 | GLN | 233 | 10.307 | 5.642 | -8.874 | 1.00 | 0.00 |
| ATOM | 480 | NE2 | GLN | 233 | 8.221 | 5.637 | -8.019 | 1.00 | 0.00 |
| ATOM | 481 | H | GLN | 233 | 10.549 | 0.640 | -6.746 | 1.00 | 0.00 |
| ATOM | 482 | N | ARG | 234 | 8.088 | -0.057 | -6.695 | 1.00 | 0.00 |
| ATOM | 483 | CA | ARG | 234 | 7.367 | -1.307 | -6.485 | 1.00 | 0.00 |
| ATOM | 484 | C | ARG | 234 | 5.845 | -1.090 | -6.342 | 1.00 | 0.00 |
| ATOM | 485 | O | ARG | 234 | 5.330 | -0.049 | -6.748 | 1.00 | 0.00 |
| ATOM | 486 | CB | ARG | 234 | 7.730 | -2.318 | -7.576 | 1.00 | 0.00 |
| ATOM | 487 | CG | ARG | 234 | 9.048 | -3.037 | -7.283 | 1.00 | 0.00 |
| ATOM | 488 | CD | ARG | 234 | 9.002 | -4.416 | -7.944 | 1.00 | 0.00 |
| ATOM | 489 | NE | ARG | 234 | 9.937 | -4.505 | -9.070 | 1.00 | 0.00 |
| ATOM | 490 | CZ | ARG | 234 | 11.263 | -4.566 | -8.900 | 1.00 | 0.00 |
| ATOM | 491 | NH1 | ARG | 234 | 11.751 | -4.685 | -7.661 | 1.00 | 0.00 |
| ATOM | 492 | NH2 | ARG | 234 | 12.089 | -4.487 | -9.954 | 1.00 | 0.00 |
| ATOM | 493 | HE | ARG | 234 | 9.565 | -4.416 | -10.004 | 1.00 | 0.00 |
| ATOM | 494 | HH21 | ARG | 234 | 11.710 | -4.427 | -10.888 | 1.00 | 0.00 |
| ATOM | 495 | HH22 | ARG | 234 | 13.093 | -4.466 | -9.818 | 1.00 | 0.00 |
| ATOM | 496 | HH11 | ARG | 234 | 11.129 | -4.814 | -6.879 | 1.00 | 0.00 |
| ATOM | 497 | HH12 | ARG | 234 | 12.739 | -4.556 | -7.495 | 1.00 | 0.00 |
| ATOM | 498 | H | ARG | 234 | 8.479 | 0.112 | -7.613 | 1.00 | 0.00 |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 499 | N | ASN | 235 | 5.153 | -2.065 | -5.727 | 1.00 | 0.00 |
| ATOM | 500 | CA | ASN | 235 | 3.753 | -2.045 | -5.267 | 1.00 | 0.00 |
| ATOM | 501 | C | ASN | 235 | 2.712 | -1.332 | -6.154 | 1.00 | 0.00 |
| ATOM | 502 | O | ASN | 235 | 2.665 | -1.690 | -7.322 | 1.00 | 0.00 |
| ATOM | 503 | CB | ASN | 235 | 3.661 | -1.706 | -3.803 | 1.00 | 0.00 |
| ATOM | 504 | CG | ASN | 235 | 4.364 | -2.678 | -2.871 | 1.00 | 0.00 |
| ATOM | 505 | OD1 | ASN | 235 | 4.952 | -3.669 | -3.296 | 1.00 | 0.00 |
| ATOM | 506 | ND2 | ASN | 235 | 4.312 | -2.367 | -1.577 | 1.00 | 0.00 |
| ATOM | 507 | H | ASN | 235 | 5.693 | -2.873 | -5.446 | 1.00 | 0.00 |
| ATOM | 508 | N | LEU | 236 | 1.834 | -0.377 | -5.772 | 1.00 | 0.00 |
| ATOM | 509 | CA | LEU | 236 | 1.578 | 0.489 | -4.609 | 1.00 | 0.00 |
| ATOM | 510 | C | LEU | 236 | 0.908 | -0.029 | -3.260 | 1.00 | 0.00 |
| ATOM | 511 | O | LEU | 236 | 1.598 | -0.823 | -2.649 | 1.00 | 0.00 |
| ATOM | 512 | CB | LEU | 236 | 2.193 | 1.891 | -4.870 | 1.00 | 0.00 |
| ATOM | 513 | CG | LEU | 236 | 3.308 | 2.518 | -4.023 | 1.00 | 0.00 |
| ATOM | 514 | CD1 | LEU | 236 | 3.104 | 4.023 | -4.239 | 1.00 | 0.00 |
| ATOM | 515 | CD2 | LEU | 236 | 3.079 | 2.194 | -2.547 | 1.00 | 0.00 |
| ATOM | 516 | H | LEU | 236 | 1.373 | 0.020 | -6.586 | 1.00 | 0.00 |
| ATOM | 517 | N | CYS | 237 | -0.298 | 0.334 | -2.711 | 1.00 | 0.00 |
| ATOM | 518 | CA | CYS | 237 | -1.183 | -0.729 | -2.136 | 1.00 | 0.00 |
| ATOM | 519 | C | CYS | 237 | -0.433 | -1.750 | -1.296 | 1.00 | 0.00 |
| ATOM | 520 | O | CYS | 237 | -0.024 | -1.471 | -0.170 | 1.00 | 0.00 |
| ATOM | 521 | CB | CYS | 237 | -2.279 | -0.238 | -1.191 | 1.00 | 0.00 |
| ATOM | 522 | SG | CYS | 237 | -3.968 | 0.155 | -1.674 | 1.00 | 0.00 |
| ATOM | 523 | LPG1 | CYS | 237 | -3.841 | 0.387 | -2.269 | 1.00 | 0.00 |
| ATOM | 524 | LPG2 | CYS | 237 | -3.841 | 0.387 | -2.269 | 1.00 | 0.00 |
| ATOM | 525 | H | CYS | 237 | -0.351 | 1.183 | -2.124 | 1.00 | 0.00 |
| ATOM | 526 | N | LEU | 238 | -0.242 | -2.918 | -1.897 | 1.00 | 0.00 |
| ATOM | 527 | CA | LEU | 238 | 0.655 | -3.954 | -1.427 | 1.00 | 0.00 |
| ATOM | 528 | C | LEU | 238 | 1.163 | -4.755 | -2.625 | 1.00 | 0.00 |
| ATOM | 529 | O | LEU | 238 | 0.506 | -4.831 | -3.664 | 1.00 | 0.00 |
| ATOM | 530 | CB | LEU | 238 | -0.036 | -4.897 | -0.433 | 1.00 | 0.00 |
| ATOM | 531 | CG | LEU | 238 | -0.169 | -4.294 | 0.966 | 1.00 | 0.00 |
| ATOM | 532 | CD1 | LEU | 238 | -0.868 | -5.287 | 1.891 | 1.00 | 0.00 |
| ATOM | 533 | CD2 | LEU | 238 | 1.199 | -3.946 | 1.550 | 1.00 | 0.00 |
| ATOM | 534 | H | LEU | 238 | -0.618 | -3.035 | -2.824 | 1.00 | 0.00 |
| ATOM | 535 | N | LEU | 239 | 2.327 | -5.384 | -2.440 | 1.00 | 0.00 |
| ATOM | 536 | CA | LEU | 239 | 2.817 | -6.483 | -3.258 | 1.00 | 0.00 |
| ATOM | 537 | C | LEU | 239 | 3.628 | -6.080 | -4.481 | 1.00 | 0.00 |
| ATOM | 538 | O | LEU | 239 | 3.171 | -5.321 | -5.334 | 1.00 | 0.00 |
| ATOM | 539 | CB | LEU | 239 | 1.740 | -7.528 | -3.528 | 1.00 | 0.00 |
| ATOM | 540 | CG | LEU | 239 | 1.909 | -8.639 | -2.496 | 1.00 | 0.00 |
| ATOM | 541 | CD1 | LEU | 239 | 0.601 | -8.863 | -1.742 | 1.00 | 0.00 |
| ATOM | 542 | CD2 | LEU | 239 | 2.335 | -9.924 | -3.198 | 1.00 | 0.00 |
| ATOM | 543 | H | LEU | 239 | 2.824 | -5.198 | -1.582 | 1.00 | 0.00 |
| ATOM | 544 | N | LYS | 240 | 4.851 | -6.614 | -4.534 | 1.00 | 0.00 |
| ATOM | 545 | CA | LYS | 240 | 5.799 | -6.378 | -5.605 | 1.00 | 0.00 |
| ATOM | 546 | C | LYS | 240 | 6.949 | -5.529 | -5.069 | 1.00 | 0.00 |
| ATOM | 547 | O | LYS | 240 | 6.976 | -4.318 | -5.266 | 1.00 | 0.00 |
| ATOM | 548 | CB | LYS | 240 | 6.263 | -7.734 | -6.123 | 1.00 | 0.00 |
| ATOM | 549 | CG | LYS | 240 | 7.251 | -7.571 | -7.291 | 1.00 | 0.00 |
| ATOM | 550 | CD | LYS | 240 | 8.006 | -8.882 | -7.496 | 1.00 | 0.00 |
| ATOM | 551 | CE | LYS | 240 | 9.512 | -8.635 | -7.487 | 1.00 | 0.00 |
| ATOM | 552 | NZ | LYS | 240 | 9.987 | -8.297 | -6.138 | 1.00 | 0.00 |
| ATOM | 553 | HZ3 | LYS | 240 | 9.271 | -8.512 | -5.459 | 1.00 | 0.00 |
| ATOM | 554 | HZ2 | LYS | 240 | 10.186 | -7.306 | -6.096 | 1.00 | 0.00 |
| ATOM | 555 | HZ1 | LYS | 240 | 10.828 | -8.811 | -5.921 | 1.00 | 0.00 |
| ATOM | 556 | H | LYS | 240 | 5.139 | -7.224 | -3.782 | 1.00 | 0.00 |
| ATOM | 557 | N | THR | 241 | 7.881 | -6.176 | -4.366 | 1.00 | 0.00 |
| ATOM | 558 | CA | THR | 241 | 8.935 | -5.530 | -3.608 | 1.00 | 0.00 |
| ATOM | 559 | C | THR | 241 | 10.061 | -5.017 | -4.495 | 1.00 | 0.00 |
| ATOM | 560 | O | THR | 241 | 10.511 | -5.705 | -5.403 | 1.00 | 0.00 |
| ATOM | 561 | CB | THR | 241 | 9.467 | -6.512 | -2.564 | 1.00 | 0.00 |
| ATOM | 562 | OG1 | THR | 241 | 9.808 | -7.739 | -3.172 | 1.00 | 0.00 |
| ATOM | 563 | CG2 | THR | 241 | 8.408 | -6.763 | -1.494 | 1.00 | 0.00 |
| ATOM | 564 | H | THR | 241 | 7.811 | -7.179 | -4.275 | 1.00 | 0.00 |
| ATOM | 565 | N | SER | 242 | 10.543 | -3.815 | -4.189 | 1.00 | 0.00 |
| ATOM | 566 | CA | SER | 242 | 11.686 | -3.203 | -4.845 | 1.00 | 0.00 |
| ATOM | 567 | C | SER | 242 | 13.018 | -3.825 | -4.400 | 1.00 | 0.00 |
| ATOM | 568 | O | SER | 242 | 13.961 | -4.651 | -3.491 | 1.00 | 0.00 |
| ATOM | 569 | CB | SER | 242 | 11.433 | -1.679 | -4.677 | 1.00 | 0.00 |
| ATOM | 570 | OG | SER | 242 | 10.927 | -1.314 | -3.500 | 1.00 | 0.00 |
| ATOM | 571 | HG | SER | 242 | 10.536 | -0.451 | -3.629 | 1.00 | 0.00 |

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|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 572 | H | SER | 242 | 10.121 | -3.301 | -3.433 | 1.00 | 0.00 |
| ATOM | 573 | N | GLU | 243 | 14.096 | -3.421 | -5.074 | 1.00 | 0.00 |
| ATOM | 574 | CA | GLU | 243 | 15.463 | -3.924 | -4.930 | 1.00 | 0.00 |
| ATOM | 575 | C | GLU | 243 | 16.173 | -3.201 | -3.819 | 1.00 | 0.00 |
| ATOM | 576 | O | GLU | 243 | 17.025 | -3.805 | -3.167 | 1.00 | 0.00 |
| ATOM | 577 | CB | GLU | 243 | 16.306 | -3.729 | -6.198 | 1.00 | 0.00 |
| ATOM | 578 | CG | GLU | 243 | 16.667 | -2.254 | -6.432 | 1.00 | 0.00 |
| ATOM | 579 | CD | GLU | 243 | 17.429 | -2.016 | -7.735 | 1.00 | 0.00 |
| ATOM | 580 | OE1 | GLU | 243 | 17.705 | -2.999 | -8.435 | 1.00 | 0.00 |
| ATOM | 581 | OE2 | GLU | 243 | 17.722 | -0.822 | -7.998 | 1.00 | 0.00 |
| ATOM | 582 | H | GLU | 243 | 13.959 | -2.682 | -5.745 | 1.00 | 0.00 |
| ATOM | 583 | N | SER | 244 | 15.801 | -1.922 | -3.628 | 1.00 | 0.00 |
| ATOM | 584 | CA | SER | 244 | 16.148 | -1.114 | -2.482 | 1.00 | 0.00 |
| ATOM | 585 | C | SER | 244 | 16.136 | -1.999 | -1.243 | 1.00 | 0.00 |
| ATOM | 586 | O | SER | 244 | 15.318 | -2.927 | -1.188 | 1.00 | 0.00 |
| ATOM | 587 | CB | SER | 244 | 17.486 | -0.419 | -2.691 | 1.00 | 0.00 |
| ATOM | 588 | OG | SER | 244 | 17.231 | 0.798 | -3.344 | 1.00 | 0.00 |
| ATOM | 589 | H | SER | 244 | 15.093 | -1.533 | -4.228 | 1.00 | 0.00 |
| ATOM | 590 | N | GLY | 245 | 17.069 | -1.682 | -0.312 | 1.00 | 0.00 |
| ATOM | 591 | CA | GLY | 245 | 17.209 | -1.988 | 1.058 | 1.00 | 0.00 |
| ATOM | 592 | C | GLY | 245 | 15.841 | -1.550 | 1.463 | 1.00 | 0.00 |
| ATOM | 593 | O | GLY | 245 | 15.488 | -0.435 | 1.794 | 1.00 | 0.00 |
| ATOM | 594 | H | GLY | 245 | 17.629 | -0.865 | -0.435 | 1.00 | 0.00 |
| ATOM | 595 | N | LEU | 246 | 15.062 | -2.443 | 1.395 | 1.00 | 0.00 |
| ATOM | 596 | CA | LEU | 246 | 14.257 | -2.565 | 2.456 | 1.00 | 0.00 |
| ATOM | 597 | C | LEU | 246 | 14.830 | -3.938 | 3.399 | 1.00 | 0.00 |
| ATOM | 598 | O | LEU | 246 | 14.218 | -4.569 | 4.406 | 1.00 | 0.00 |
| ATOM | 599 | CB | LEU | 246 | 13.130 | -2.568 | 1.278 | 1.00 | 0.00 |
| ATOM | 600 | CG | LEU | 246 | 11.823 | -1.707 | 1.266 | 1.00 | 0.00 |
| ATOM | 601 | CD1 | LEU | 246 | 11.202 | -1.722 | -0.173 | 1.00 | 0.00 |
| ATOM | 602 | CD2 | LEU | 246 | 12.335 | -0.380 | 1.719 | 1.00 | 0.00 |
| ATOM | 603 | N | PRO | 247 | 14.743 | -4.728 | 2.392 | 1.00 | 0.00 |
| ATOM | 604 | CA | PRO | 247 | 13.223 | -4.611 | 2.461 | 1.00 | 0.00 |
| ATOM | 605 | C | PRO | 247 | 12.240 | -3.628 | 3.441 | 1.00 | 0.00 |
| ATOM | 606 | O | PRO | 247 | 12.824 | -2.914 | 4.273 | 1.00 | 0.00 |
| ATOM | 607 | CB | PRO | 247 | 13.957 | -2.569 | 2.914 | 1.00 | 0.00 |
| ATOM | 608 | CG | PRO | 247 | 15.449 | -2.497 | 2.631 | 1.00 | 0.00 |
| ATOM | 609 | CD | PRO | 247 | 15.939 | -3.910 | 2.357 | 1.00 | 0.00 |
| ATOM | 610 | N | SER | 248 | 11.028 | -3.341 | 3.436 | 1.00 | 0.00 |
| ATOM | 611 | CA | SER | 248 | 10.344 | -2.880 | 4.671 | 1.00 | 0.00 |
| ATOM | 612 | C | SER | 248 | 9.981 | -1.419 | 4.798 | 1.00 | 0.00 |
| ATOM | 613 | O | SER | 248 | 10.806 | -0.559 | 5.081 | 1.00 | 0.00 |
| ATOM | 614 | CB | SER | 248 | 10.815 | -3.586 | 5.956 | 1.00 | 0.00 |
| ATOM | 615 | OG | SER | 248 | 10.762 | -5.004 | 5.836 | 1.00 | 0.00 |
| ATOM | 616 | H | SER | 248 | 10.629 | -3.796 | 2.628 | 1.00 | 0.00 |
| ATOM | 617 | N | THR | 249 | 8.696 | -1.185 | 4.570 | 1.00 | 0.00 |
| ATOM | 618 | CA | THR | 249 | 8.012 | 0.046 | 4.865 | 1.00 | 0.00 |
| ATOM | 619 | C | THR | 249 | 8.031 | 0.271 | 6.375 | 1.00 | 0.00 |
| ATOM | 620 | O | THR | 249 | 8.026 | -0.677 | 7.165 | 1.00 | 0.00 |
| ATOM | 621 | CB | THR | 249 | 6.567 | -0.150 | 4.372 | 1.00 | 0.00 |
| ATOM | 622 | OG1 | THR | 249 | 6.491 | -1.540 | 4.064 | 1.00 | 0.00 |
| ATOM | 623 | CG2 | THR | 249 | 6.305 | 0.543 | 3.033 | 1.00 | 0.00 |
| ATOM | 624 | N | ARG | 250 | 8.054 | 1.544 | 6.762 | 1.00 | 0.00 |
| ATOM | 625 | CA | ARG | 250 | 7.984 | 1.926 | 8.154 | 1.00 | 0.00 |
| ATOM | 626 | C | ARG | 250 | 6.561 | 1.756 | 8.672 | 1.00 | 0.00 |
| ATOM | 627 | O | ARG | 250 | 5.629 | 2.364 | 8.147 | 1.00 | 0.00 |
| ATOM | 628 | CB | ARG | 250 | 8.467 | 3.362 | 8.303 | 1.00 | 0.00 |
| ATOM | 629 | CG | ARG | 250 | 8.586 | 3.702 | 9.783 | 1.00 | 0.00 |
| ATOM | 630 | CD | ARG | 250 | 8.666 | 5.217 | 9.900 | 1.00 | 0.00 |
| ATOM | 631 | NE | ARG | 250 | 8.423 | 5.667 | 11.271 | 1.00 | 0.00 |
| ATOM | 632 | CZ | ARG | 250 | 8.737 | 6.903 | 11.688 | 1.00 | 0.00 |
| ATOM | 633 | NH1 | ARG | 250 | 9.277 | 7.782 | 10.830 | 1.00 | 0.00 |
| ATOM | 634 | NH2 | ARG | 250 | 8.512 | 7.257 | 12.961 | 1.00 | 0.00 |
| ATOM | 635 | HE | ARG | 250 | 7.996 | 5.016 | 11.914 | 1.00 | 0.00 |
| ATOM | 636 | HH21 | ARG | 250 | 8.104 | 6.595 | 13.605 | 1.00 | 0.00 |
| ATOM | 637 | HH22 | ARG | 250 | 8.753 | 8.185 | 13.278 | 1.00 | 0.00 |
| ATOM | 638 | HH11 | ARG | 250 | 9.436 | 7.510 | 9.871 | 1.00 | 0.00 |
| ATOM | 639 | HH12 | ARG | 250 | 9.518 | 8.713 | 11.136 | 1.00 | 0.00 |
| ATOM | 640 | H | ARG | 250 | 6.073 | 2.267 | 6.059 | 1.00 | 0.00 |
| ATOM | 641 | N | ILE | 251 | 6.402 | 0.928 | 8.708 | 1.00 | 0.00 |
| ATOM | 642 | CA | ILE | 251 | 5.102 | 0.701 | 10.311 | 1.00 | 0.00 |
| ATOM | 643 | C | ILE | 251 | 5.175 | 0.642 | 11.836 | 1.00 | 0.00 |
| ATOM | 644 | O | ILE | 251 | 4.756 | 1.589 | 12.499 | 1.00 | 0.00 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| ATOM | 645 | CB | ILE | 251 | 4.382 | -0.492 | 9.656 | 1.00 | 0.00 |
| ATOM | 646 | CG1 | ILE | 251 | 5.248 | -1.752 | 9.708 | 1.00 | 0.00 |
| ATOM | 647 | CG2 | ILE | 251 | 3.948 | -0.154 | 8.228 | 1.00 | 0.00 |
| ATOM | 648 | CD1 | ILE | 251 | 4.532 | -2.938 | 9.057 | 1.00 | 0.00 |
| ATOM | 649 | H | ILE | 251 | 7.202 | 0.448 | 10.094 | 1.00 | 0.00 |
| ATOM | 650 | N | LYS | 252 | 5.683 | -0.463 | 12.392 | 1.00 | 0.00 |
| ATOM | 651 | CA | LYS | 252 | 5.685 | -0.680 | 13.827 | 1.00 | 0.00 |
| ATOM | 652 | C | LYS | 252 | 6.616 | -1.829 | 14.190 | 1.00 | 0.00 |
| ATOM | 653 | O | LYS | 252 | 7.587 | -1.625 | 14.918 | 1.00 | 0.00 |
| ATOM | 654 | CB | LYS | 252 | 4.248 | -0.953 | 14.311 | 1.00 | 0.00 |
| ATOM | 655 | CG | LYS | 252 | 4.137 | -0.776 | 15.826 | 1.00 | 0.00 |
| ATOM | 656 | CD | LYS | 252 | 5.522 | -0.659 | 16.468 | 1.00 | 0.00 |
| ATOM | 657 | CE | LYS | 252 | 5.410 | -0.482 | 17.983 | 1.00 | 0.00 |
| ATOM | 658 | NZ | LYS | 252 | 6.747 | -0.371 | 18.589 | 1.00 | 0.00 |
| ATOM | 659 | H | LYS | 252 | 6.036 | -1.202 | 11.802 | 1.00 | 0.00 |
| ATOM | 660 | N | LYS | 253 | 6.313 | -3.031 | 13.686 | 1.00 | 0.00 |
| ATOM | 661 | CA | LYS | 253 | 7.107 | -4.220 | 13.938 | 1.00 | 0.00 |
| ATOM | 662 | C | LYS | 253 | 8.538 | -4.066 | 13.435 | 1.00 | 0.00 |
| ATOM | 663 | O | LYS | 253 | 8.793 | -3.355 | 12.463 | 1.00 | 0.00 |
| ATOM | 664 | CB | LYS | 253 | 6.424 | -5.451 | 13.314 | 1.00 | 0.00 |
| ATOM | 665 | CG | LYS | 253 | 5.153 | -5.821 | 14.082 | 1.00 | 0.00 |
| ATOM | 666 | CD | LYS | 253 | 4.555 | -7.128 | 13.556 | 1.00 | 0.00 |
| ATOM | 667 | CE | LYS | 253 | 4.137 | -8.042 | 14.709 | 1.00 | 0.00 |
| ATOM | 668 | NZ | LYS | 253 | 3.415 | -9.219 | 14.197 | 1.00 | 0.00 |
| ATOM | 669 | H | LYS | 253 | 5.491 | -3.129 | 13.107 | 1.00 | 0.00 |
| ATOM | 670 | N | SER | 254 | 9.467 | -4.730 | 14.130 | 1.00 | 0.00 |
| ATOM | 671 | CA | SER | 254 | 10.893 | -4.649 | 13.865 | 1.00 | 0.00 |
| ATOM | 672 | C | SER | 254 | 11.248 | -5.052 | 12.437 | 1.00 | 0.00 |
| ATOM | 673 | O | SER | 254 | 10.779 | -6.071 | 11.932 | 1.00 | 0.00 |
| ATOM | 674 | CB | SER | 254 | 11.663 | -5.458 | 14.925 | 1.00 | 0.00 |
| ATOM | 675 | OG | SER | 254 | 12.165 | -4.629 | 15.969 | 1.00 | 0.00 |
| ATOM | 676 | H | SER | 254 | 9.172 | -5.289 | 14.918 | 1.00 | 0.00 |
| ATOM | 677 | N | LYS | 255 | 12.115 | -4.250 | 11.812 | 1.00 | 0.00 |
| ATOM | 678 | CA | LYS | 255 | 12.760 | -4.621 | 10.569 | 1.00 | 0.00 |
| ATOM | 679 | C | LYS | 255 | 13.918 | -5.557 | 10.892 | 1.00 | 0.00 |
| ATOM | 680 | O | LYS | 255 | 14.866 | -5.167 | 11.572 | 1.00 | 0.00 |
| ATOM | 681 | CB | LYS | 255 | 13.250 | -3.358 | 9.836 | 1.00 | 0.00 |
| ATOM | 682 | CG | LYS | 255 | 13.936 | -3.721 | 8.518 | 1.00 | 0.00 |
| ATOM | 683 | CD | LYS | 255 | 14.422 | -2.466 | 7.789 | 1.00 | 0.00 |
| ATOM | 684 | CE | LYS | 255 | 15.109 | -2.829 | 6.471 | 1.00 | 0.00 |
| ATOM | 685 | NZ | LYS | 255 | 15.572 | -1.615 | 5.760 | 1.00 | 0.00 |
| ATOM | 686 | H | LYS | 255 | 12.446 | -3.420 | 12.284 | 1.00 | 0.00 |
| ATOM | 687 | N | ALA | 256 | 13.817 | -6.806 | 10.431 | 1.00 | 0.00 |
| ATOM | 688 | CA | ALA | 256 | 14.802 | -7.828 | 10.729 | 1.00 | 0.00 |
| ATOM | 689 | C | ALA | 256 | 15.023 | -8.716 | 9.514 | 1.00 | 0.00 |
| ATOM | 690 | O | ALA | 256 | 14.057 | -9.139 | 8.878 | 1.00 | 0.00 |
| ATOM | 691 | CB | ALA | 256 | 14.345 | -8.652 | 11.929 | 1.00 | 0.00 |
| ATOM | 692 | H | ALA | 256 | 13.017 | -7.064 | 9.870 | 1.00 | 0.00 |
| ATOM | 693 | N | LEU | 257 | 16.299 | -8.981 | 9.199 | 1.00 | 0.00 |
| ATOM | 694 | CA | LEU | 257 | 16.736 | -9.736 | 8.029 | 1.00 | 0.00 |
| ATOM | 695 | C | LEU | 257 | 16.594 | -8.912 | 6.759 | 1.00 | 0.00 |
| ATOM | 696 | O | LEU | 257 | 17.580 | -8.601 | 6.093 | 1.00 | 0.00 |
| ATOM | 697 | CB | LEU | 257 | 16.061 | -11.118 | 7.947 | 1.00 | 0.00 |
| ATOM | 698 | CG | LEU | 257 | 16.351 | -12.076 | 9.105 | 1.00 | 0.00 |
| ATOM | 699 | CD1 | LEU | 257 | 15.160 | -12.154 | 10.062 | 1.00 | 0.00 |
| ATOM | 700 | CD2 | LEU | 257 | 16.761 | -13.455 | 8.585 | 1.00 | 0.00 |
| ATOM | 701 | H | LEU | 257 | 17.024 | -8.606 | 9.794 | 1.00 | 0.00 |
| ATOM | 702 | N | SER | 258 | 15.363 | -8.505 | 6.460 | 1.00 | 0.00 |
| ATOM | 703 | CA | SER | 258 | 15.095 | -7.393 | 5.595 | 1.00 | 0.00 |
| ATOM | 704 | C | SER | 258 | 15.858 | -6.159 | 6.163 | 1.00 | 0.00 |
| ATOM | 705 | O | SER | 258 | 15.989 | -5.994 | 7.392 | 1.00 | 0.00 |
| ATOM | 706 | CB | SER | 258 | 13.554 | -7.327 | 5.494 | 1.00 | 0.00 |
| ATOM | 707 | OG | SER | 258 | 12.953 | -8.569 | 5.075 | 1.00 | 0.00 |
| ATOM | 708 | HG | SER | 258 | 12.045 | -8.389 | 4.799 | 1.00 | 0.00 |
| ATOM | 709 | H | SER | 258 | 14.581 | -8.797 | 7.031 | 1.00 | 0.00 |
| ATOM | 710 | N | GLY | 259 | 16.428 | -5.338 | 5.234 | 1.00 | 0.00 |
| ATOM | 711 | CA | GLY | 259 | 16.803 | -3.904 | 5.425 | 1.00 | 0.00 |
| ATOM | 712 | C | GLY | 259 | 15.798 | -2.862 | 5.997 | 1.00 | 0.00 |
| ATOM | 713 | O | GLY | 259 | 14.832 | -3.188 | 6.682 | 1.00 | 0.00 |
| ATOM | 714 | H | GLY | 259 | 15.961 | -5.509 | 4.368 | 1.00 | 0.00 |
| ATOM | 715 | N | PHE | 260 | 16.125 | -1.593 | 5.737 | 1.00 | 0.00 |
| ATOM | 716 | CA | PHE | 260 | 15.508 | -0.436 | 6.360 | 1.00 | 0.00 |
| ATOM | 717 | C | PHE | 260 | 16.089 | 0.838 | 5.752 | 1.00 | 0.00 |

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ATOM    716  O   PHE   260      17.202   1.238   6.092  1.00  0.00
ATOM    719  CB  PHE   260      15.745  -0.484   7.881  1.00  0.00
ATOM    720  CG  PHE   260      15.177   0.700   8.651  1.00  0.00
ATOM    721  CD1 PHE   260      13.792   0.984   8.606  1.00  0.00
ATOM    722  CD2 PHE   260      16.035   1.529   9.410  1.00  0.00
ATOM    723  CE1 PHE   260      13.270   2.085   9.318  1.00  0.00
ATOM    724  CE2 PHE   260      15.512   2.630  10.121  1.00  0.00
ATOM    725  CZ  PHE   260      14.130   2.908  10.075  1.00  0.00
ATOM    726  H   PHE   260      16.923  -1.427   5.137  1.00  0.00
ATOM    727  N   SER   261      15.320   1.476   4.864  1.00  0.00
ATOM    728  CA  SER   261      15.673   2.780   4.327  1.00  0.00
ATOM    729  C   SER   261      14.470   3.530   3.751  1.00  0.00
ATOM    730  O   SER   261      13.329   3.093   3.896  1.00  0.00
ATOM    731  CB  SER   261      16.871   2.703   3.376  1.00  0.00
ATOM    732  OG  SER   261      16.596   1.901   2.252  1.00  0.00
ATOM    733  HG  SER   261      16.853   0.997   2.454  1.00  0.00
ATOM    734  H   SER   261      14.420   1.088   4.620  1.00  0.00
ATOM    735  N   LEU   262      14.733   4.683   3.125  1.00  0.00
ATOM    736  CA  LEU   262      13.699   5.609   2.692  1.00  0.00
ATOM    737  C   LEU   262      13.023   5.163   1.402  1.00  0.00
ATOM    738  O   LEU   262      13.624   5.222   0.331  1.00  0.00
ATOM    739  CB  LEU   262      14.302   7.014   2.505  1.00  0.00
ATOM    740  CG  LEU   262      14.632   7.779   3.788  1.00  0.00
ATOM    741  CD1 LEU   262      13.483   8.708   4.183  1.00  0.00
ATOM    742  CD2 LEU   262      15.007   6.818   4.918  1.00  0.00
ATOM    743  H   LEU   262      15.693   4.980   3.028  1.00  0.00
ATOM    744  N   GLN   263      11.746   4.782   1.502  1.00  0.00
ATOM    745  CA  GLN   263      10.901   4.646   0.330  1.00  0.00
ATOM    746  C   GLN   263      10.115   5.935   0.106  1.00  0.00
ATOM    747  O   GLN   263       9.526   6.480   1.039  1.00  0.00
ATOM    748  CB  GLN   263       9.996   3.405   0.441  1.00  0.00
ATOM    749  CG  GLN   263       9.007   3.550   1.600  1.00  0.00
ATOM    750  CD  GLN   263       8.396   2.197   1.972  1.00  0.00
ATOM    751  OE1 GLN   263       7.313   2.107   2.526  1.00  0.00
ATOM    752  NE2 GLN   263       9.149   1.153   1.637  1.00  0.00
ATOM    753  H   GLN   263      11.308   4.731   2.410  1.00  0.00
ATOM    754  N   SER   264      10.122   6.431  -1.134  1.00  0.00
ATOM    755  CA  SER   264       9.404   7.642  -1.482  1.00  0.00
ATOM    756  C   SER   264       8.655   7.486  -2.800  1.00  0.00
ATOM    757  O   SER   264       9.186   6.936  -3.764  1.00  0.00
ATOM    758  CB  SER   264      10.364   8.846  -1.515  1.00  0.00
ATOM    759  OG  SER   264      10.310   9.605  -0.310  1.00  0.00
ATOM    760  H   SER   264      10.627   5.948  -1.864  1.00  0.00
ATOM    761  N   CYS   265       7.423   8.013  -2.829  1.00  0.00
ATOM    762  CA  CYS   265       6.608   8.177  -4.025  1.00  0.00
ATOM    763  C   CYS   265       7.151   9.268  -4.953  1.00  0.00
ATOM    764  O   CYS   265       8.333   9.598  -4.877  1.00  0.00
ATOM    765  CB  CYS   265       6.290   6.835  -4.702  1.00  0.00
ATOM    766  SG  CYS   265       6.101   6.850  -6.507  1.00  0.00
ATOM    767 LPG1 CYS   265       6.442   7.417  -6.623  1.00  0.00
ATOM    768 LPG2 CYS   265       5.951   6.184  -6.576  1.00  0.00
ATOM    769  OXT CYS   265       6.241   9.935  -5.716  1.00  0.00
ATOM    770  H   CYS   265       7.069   8.432  -1.981  1.00  0.00
TER     771      CYS   265
CONECT   12   11   13   14  766
CONECT   68   67   69   71
CONECT   71   68   72
CONECT  194  193  195  197
CONECT  197  194  198
CONECT  240  239  241  242  522
CONECT  275  274  276  277  328
CONECT  312  311  313  315
CONECT  315  312  316
CONECT  328  275  327  329  330
CONECT  440  439  441  443
CONECT  443  440  444
CONECT  522  240  521  523  524
CONECT  604  603  605  607
CONECT  607  604  608
CONECT  766   12  765  767  768
MASTER        0    0    0    0    0    0    0    0  770    1   16    7
END
```

APPENDIX 2

Factor XI Heavy Chain Domain A1

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ATOM      1  N   GLU     1     155.502    3.466  -12.472
ATOM      2  HN  GLU     1     156.178    4.244  -12.172
ATOM      3  HN  GLU     1     155.722    3.318  -13.473
ATOM      4  HN  GLU     1     154.618    3.716  -12.305
ATOM      5  CA  GLU     1     155.885    2.210  -11.762
ATOM      6  C   GLU     1     156.562    2.369  -10.453
ATOM      7  O   GLU     1     157.713    1.862  -10.388
ATOM      8  CB  GLU     1     154.648    1.284  -11.743
ATOM      9  CG  GLU     1     154.949   -0.199  -11.441
ATOM     10  CD  GLU     1     153.782   -1.021  -11.086
ATOM     11  OE1 GLU     1     153.604   -1.365   -9.898
ATOM     12  OE2 GLU     1     152.955   -1.369  -11.974
ATOM     13  N   CYS     2     156.118    2.949   -9.339
ATOM     14  HN  CYS     2     156.695    2.937   -8.596
ATOM     15  CA  CYS     2     154.884    3.576   -9.172
ATOM     16  C   CYS     2     153.796    2.787   -8.544
ATOM     17  O   CYS     2     153.946    2.209   -7.446
ATOM     18  CB  CYS     2     155.075    4.997   -8.614
ATOM     19  SG  CYS     2     155.135    5.111   -6.849
ATOM     20  N   VAL     3     152.578    2.596   -9.016
ATOM     21  HN  VAL     3     152.002    2.129   -8.439
ATOM     22  CA  VAL     3     152.016    2.970  -10.231
ATOM     23  C   VAL     3     152.297    4.239  -10.646
ATOM     24  O   VAL     3     152.731    4.208  -12.015
ATOM     25  CB  VAL     3     150.650    2.274  -10.451
ATOM     26  CG1 VAL     3     149.381    3.139  -10.483
ATOM     27  CG2 VAL     3     150.656    1.399  -11.710
ATOM     28  N   THR     4     152.193    5.638  -10.410
ATOM     29  HN  THR     4     152.282    6.174  -11.095
ATOM     30  CA  THR     4     151.998    6.118   -9.146
ATOM     31  C   THR     4     151.164    5.502   -8.090
ATOM     32  O   THR     4     149.913    5.459   -8.245
ATOM     33  CB  THR     4     151.882    7.651   -8.355
ATOM     34  OG1 THR     4     152.452    8.394   -8.291
ATOM     35  HOG1 THR     4     151.971    8.213   -7.456
ATOM     36  CG2 THR     4     150.512    8.260   -9.703
ATOM     37  N   GLN     5     151.782    5.013   -7.005
ATOM     38  HN  GLN     5     152.719    5.098   -6.964
ATOM     39  CA  GLN     5     151.136    4.408   -5.925
ATOM     40  C   GLN     5     151.342    4.870   -4.534
ATOM     41  O   GLN     5     152.411    5.374   -4.099
ATOM     42  CB  GLN     5     151.002    2.869   -6.084
ATOM     43  CG  GLN     5     149.616    2.421   -6.502
ATOM     44  CD  GLN     5     148.423    3.029   -5.991
ATOM     45  OE1 GLN     5     148.212    3.038   -4.756
ATOM     46  NE2 GLN     5     147.525    3.602   -6.750
ATOM     47  HNE1 GLN     5     147.580    3.544   -7.656
ATOM     48  HNE2 GLN     5     146.827    4.079   -6.342
ATOM     49  N   LEU     6     150.251    4.705   -3.762
ATOM     50  HN  LEU     6     149.592    4.193   -4.143
ATOM     51  CA  LEU     6     149.977    5.145   -2.479
ATOM     52  C   LEU     6     148.624    5.750   -2.402
ATOM     53  O   LEU     6     148.561    6.765   -1.665
ATOM     54  CB  LEU     6     150.081    3.938   -1.525
ATOM     55  CG  LEU     6     151.095    4.158   -0.401
ATOM     56  CD1 LEU     6     150.405    4.024    0.960
ATOM     57  CD2 LEU     6     152.198    3.105   -0.490
ATOM     58  N   LEU     7     147.555    5.751   -3.057
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| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ATOM | 59 | HN | LEU | 7 | 147.772 | 4.532 | -3.620 |
| ATOM | 60 | CA | LEU | 7 | 146.195 | 5.609 | -3.102 |
| ATOM | 61 | C | LEU | 7 | 145.476 | 4.852 | -4.182 |
| ATOM | 62 | O | LEU | 7 | 145.529 | 5.277 | -5.385 |
| ATOM | 63 | CB | LEU | 7 | 145.787 | 7.101 | -2.951 |
| ATOM | 64 | CG | LEU | 7 | 146.325 | 8.072 | -4.016 |
| ATOM | 65 | CD1 | LEU | 7 | 145.169 | 8.619 | -4.859 |
| ATOM | 66 | CD2 | LEU | 7 | 147.021 | 9.261 | -3.351 |
| ATOM | 67 | N | LYS | 8 | 144.765 | 3.799 | -3.866 |
| ATOM | 68 | HN | LYS | 8 | 144.763 | 3.509 | -2.974 |
| ATOM | 69 | CA | LYS | 8 | 143.993 | 3.023 | -4.739 |
| ATOM | 70 | C | LYS | 8 | 144.410 | 1.608 | -4.382 |
| ATOM | 71 | O | LYS | 8 | 144.485 | 0.852 | -3.374 |
| ATOM | 72 | CB | LYS | 8 | 142.513 | 3.214 | -4.344 |
| ATOM | 73 | CG | LYS | 8 | 141.465 | 2.712 | -5.371 |
| ATOM | 74 | CD | LYS | 8 | 140.991 | 1.325 | -4.946 |
| ATOM | 75 | CE | LYS | 8 | 140.023 | 0.708 | -5.960 |
| ATOM | 76 | NZ | LYS | 8 | 140.186 | -0.739 | -5.876 |
| ATOM | 77 | HNZ1 | LYS | 8 | 139.435 | -1.221 | -6.371 |
| ATOM | 78 | HNZ2 | LYS | 8 | 140.189 | -0.978 | -4.884 |
| ATOM | 79 | HNZ3 | LYS | 8 | 141.094 | -0.957 | -6.265 |
| ATOM | 80 | N | ASP | 9 | 144.672 | 1.200 | -6.124 |
| ATOM | 81 | HN | ASP | 9 | 144.709 | 1.881 | -6.772 |
| ATOM | 82 | CA | ASP | 9 | 144.691 | -0.101 | -6.603 |
| ATOM | 83 | C | ASP | 9 | 143.845 | -1.107 | -6.787 |
| ATOM | 84 | O | ASP | 9 | 142.831 | -1.146 | -7.034 |
| ATOM | 85 | CB | ASP | 9 | 146.376 | -0.532 | -6.713 |
| ATOM | 86 | CG | ASP | 9 | 147.134 | -0.760 | -5.485 |
| ATOM | 87 | OD1 | ASP | 9 | 146.805 | -1.555 | -4.683 |
| ATOM | 88 | OD2 | ASP | 9 | 148.133 | -0.072 | -5.245 |
| ATOM | 89 | N | THR | 10 | 143.988 | -1.917 | -5.243 |
| ATOM | 90 | HN | THR | 10 | 144.876 | -1.939 | -4.842 |
| ATOM | 91 | CA | THR | 10 | 143.038 | -2.694 | -4.954 |
| ATOM | 92 | C | THR | 10 | 142.222 | -3.760 | -5.185 |
| ATOM | 93 | O | THR | 10 | 140.988 | -3.693 | -4.955 |
| ATOM | 94 | CB | THR | 10 | 143.281 | -2.906 | -3.043 |
| ATOM | 95 | OG1 | THR | 10 | 143.021 | -1.706 | -2.823 |
| ATOM | 96 | HOG1 | THR | 10 | 142.094 | -1.453 | -2.869 |
| ATOM | 97 | CG2 | THR | 10 | 144.589 | -3.580 | -2.603 |
| ATOM | 98 | N | CYS | 11 | 142.534 | -4.792 | -5.671 |
| ATOM | 99 | HN | CYS | 11 | 141.780 | -5.203 | -6.365 |
| ATOM | 100 | CA | CYS | 11 | 143.754 | 5.387 | -5.327 |
| ATOM | 101 | C | CYS | 11 | 144.168 | 6.599 | -5.532 |
| ATOM | 102 | O | CYS | 11 | 144.496 | 7.589 | -6.301 |
| ATOM | 103 | CB | CYS | 11 | 144.945 | -4.506 | -6.751 |
| ATOM | 104 | SG | CYS | 11 | 145.271 | -4.699 | -8.511 |
| ATOM | 105 | HSG | CYS | 11 | 145.380 | 3.913 | -8.569 |
| ATOM | 106 | N | PHE | 12 | 144.192 | -6.621 | -4.282 |
| ATOM | 107 | HN | PHE | 12 | 143.821 | -5.378 | -3.818 |
| ATOM | 108 | CA | PHE | 12 | 144.726 | -7.637 | -3.493 |
| ATOM | 109 | C | PHE | 12 | 143.768 | -8.156 | -2.454 |
| ATOM | 110 | O | PHE | 12 | 143.307 | -7.402 | -1.561 |
| ATOM | 111 | CB | PHE | 12 | 146.072 | -7.196 | -2.846 |
| ATOM | 112 | CG | PHE | 12 | 147.138 | 6.762 | -3.702 |
| ATOM | 113 | CD1 | PHE | 12 | 147.545 | -5.403 | -3.708 |
| ATOM | 114 | CD2 | PHE | 12 | 147.754 | 7.675 | -4.619 |
| ATOM | 115 | CE1 | PHE | 12 | 148.577 | -4.953 | -4.586 |
| ATOM | 116 | CE2 | PHE | 12 | 148.792 | -7.229 | -5.514 |
| ATOM | 117 | CZ | PHE | 12 | 149.197 | -5.378 | -5.469 |
| ATOM | 118 | N | GLU | 13 | 143.315 | 9.401 | -2.052 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ATOM | 119 | HN | GLU | 13 | 142.620 | -9.571 | -1.772 | |
| ATOM | 120 | CA | GLU | 13 | 143.776 | -10.489 | -3.121 | |
| ATOM | 121 | C | GLU | 13 | 142.962 | -10.880 | -4.288 | |
| ATOM | 122 | O | GLU | 13 | 141.863 | -11.490 | -4.144 | |
| ATOM | 123 | CB | GLU | 13 | 144.145 | -11.635 | -2.161 | |
| ATOM | 124 | CG | GLU | 13 | 145.433 | -12.354 | -2.592 | |
| ATOM | 125 | CD | GLU | 13 | 146.631 | -11.528 | -2.433 | |
| ATOM | 126 | OE1 | GLU | 13 | 147.331 | -11.595 | -1.401 | |
| ATOM | 127 | OE2 | GLU | 13 | 146.980 | -10.728 | -3.324 | |
| ATOM | 128 | N | GLY | 14 | 143.486 | -10.540 | -5.461 | |
| ATOM | 129 | HN | GLY | 14 | 144.265 | -10.016 | -5.433 | |
| ATOM | 130 | CA | GLY | 14 | 143.018 | -10.858 | -6.738 | |
| ATOM | 131 | C | GLY | 14 | 141.920 | -10.013 | -7.226 | |
| ATOM | 132 | O | GLY | 14 | 140.812 | -10.594 | -7.395 | |
| ATOM | 133 | N | GLY | 15 | 142.145 | -8.716 | -7.456 | |
| ATOM | 134 | HN | GLY | 15 | 142.963 | -8.373 | -7.148 | |
| ATOM | 135 | CA | GLY | 15 | 141.294 | -7.807 | -8.091 | |
| ATOM | 136 | C | GLY | 15 | 140.238 | -7.233 | -7.247 | |
| ATOM | 137 | O | GLY | 15 | 140.177 | -5.981 | -7.166 | |
| ATOM | 138 | N | ASP | 16 | 139.419 | -8.069 | -6.628 | |
| ATOM | 139 | HN | ASP | 16 | 139.671 | -8.567 | -6.720 | |
| ATOM | 140 | CA | ASP | 16 | 138.286 | -7.734 | -5.897 | |
| ATOM | 141 | C | ASP | 16 | 138.375 | -7.886 | -4.426 | |
| ATOM | 142 | O | ASP | 16 | 138.640 | -8.981 | -3.859 | |
| ATOM | 143 | CB | ASP | 16 | 137.033 | -8.351 | -6.540 | |
| ATOM | 144 | CG | ASP | 16 | 136.512 | -7.501 | -7.612 | |
| ATOM | 145 | OD1 | ASP | 16 | 135.536 | -6.754 | -7.389 | |
| ATOM | 146 | OD2 | ASP | 16 | 137.031 | -7.514 | -8.752 | |
| ATOM | 147 | N | ILE | 17 | 138.180 | -5.896 | -3.569 | |
| ATOM | 148 | HN | ILE | 17 | 138.170 | -7.190 | -2.677 | |
| ATOM | 149 | CA | ILE | 17 | 137.990 | -5.526 | -3.626 | |
| ATOM | 150 | C | ILE | 17 | 138.187 | -4.673 | -2.636 | |
| ATOM | 151 | O | ILE | 17 | 137.389 | -4.773 | -1.666 | |
| ATOM | 152 | CB | ILE | 17 | 136.758 | -5.173 | -4.715 | |
| ATOM | 153 | CG1 | ILE | 17 | 136.766 | -3.743 | -5.260 | |
| ATOM | 154 | CG2 | ILE | 17 | 135.364 | -5.486 | -4.140 | |
| ATOM | 155 | CD1 | ILE | 17 | 137.529 | -3.639 | -6.606 | |
| ATOM | 156 | N | THR | 18 | 139.202 | -3.814 | -2.690 | |
| ATOM | 157 | HN | THR | 18 | 139.785 | -3.808 | -3.368 | |
| ATOM | 158 | CA | THR | 18 | 139.468 | -2.898 | -1.596 | |
| ATOM | 159 | C | THR | 18 | 139.489 | -1.461 | -2.018 | |
| ATOM | 160 | O | THR | 18 | 140.263 | -1.089 | -2.921 | |
| ATOM | 161 | CB | THR | 18 | 140.520 | -3.227 | -0.515 | |
| ATOM | 162 | OG1 | THR | 18 | 141.493 | -4.220 | -0.807 | |
| ATOM | 163 | HOG1 | THR | 18 | 142.251 | -4.068 | -0.205 | |
| ATOM | 164 | CG2 | THR | 18 | 139.844 | -3.581 | 0.811 | |
| ATOM | 165 | N | THR | 19 | 138.734 | -0.517 | -1.517 | |
| ATOM | 166 | HN | THR | 19 | 138.733 | 0.297 | -1.987 | |
| ATOM | 167 | CA | THR | 19 | 137.943 | -0.551 | -0.364 | |
| ATOM | 168 | C | THR | 19 | 136.796 | -1.486 | -0.274 | |
| ATOM | 169 | O | THR | 19 | 136.739 | -2.160 | 0.783 | |
| ATOM | 170 | CB | THR | 19 | 137.723 | 0.911 | 0.100 | |
| ATOM | 171 | OG1 | THR | 19 | 137.773 | 1.050 | 1.510 | |
| ATOM | 172 | HOG1 | THR | 19 | 138.467 | 0.460 | 1.898 | |
| ATOM | 173 | CG2 | THR | 19 | 136.504 | 1.684 | -0.436 | |
| ATOM | 174 | N | VAL | 20 | 135.808 | -1.577 | -1.263 | |
| ATOM | 175 | HN | VAL | 20 | 136.213 | -1.292 | -2.106 | |
| ATOM | 176 | CA | VAL | 20 | 134.578 | -2.011 | -1.280 | |
| ATOM | 177 | C | VAL | 20 | 134.128 | -3.255 | -0.547 | |
| ATOM | 178 | O | VAL | 20 | 133.012 | -3.129 | 0.026 | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| ATOM | 179 | CB | VAL | 20 | 133.843 | -1.507 | -2.488 | |
| ATOM | 180 | CG1 | VAL | 20 | 133.315 | -2.553 | -3.482 | |
| ATOM | 181 | CG2 | VAL | 20 | 132.723 | -0.523 | -2.126 | |
| ATOM | 182 | N | PHE | 21 | 134.805 | -4.408 | -0.526 | |
| ATOM | 183 | HN | PHE | 21 | 135.640 | -4.462 | -0.955 | |
| ATOM | 184 | CA | PHE | 21 | 134.384 | -5.587 | | 0.103 |
| ATOM | 185 | C | PHE | 21 | 134.597 | -5.542 | | 1.564 |
| ATOM | 186 | O | PHE | 21 | 135.725 | -5.770 | | 2.091 |
| ATOM | 187 | CB | PHE | 21 | 134.873 | -6.843 | -0.645 | |
| ATOM | 188 | CG | PHE | 21 | 134.191 | -8.072 | -0.223 | |
| ATOM | 189 | CD1 | PHE | 21 | 134.845 | -8.955 | | 0.677 |
| ATOM | 190 | CD2 | PHE | 21 | 132.892 | -8.372 | -0.711 | |
| ATOM | 191 | CE1 | PHE | 21 | 134.194 | -10.138 | | 1.101 |
| ATOM | 192 | CE2 | PHE | 21 | 132.237 | -9.554 | -0.269 | |
| ATOM | 193 | CZ | PHE | 21 | 132.893 | -10.425 | | 0.618 |
| ATOM | 194 | N | THR | 22 | 133.509 | -5.233 | | 2.266 |
| ATOM | 195 | HN | THR | 22 | 132.701 | -5.247 | | 1.787 |
| ATOM | 196 | CA | THR | 22 | 133.421 | -4.077 | | 3.625 |
| ATOM | 197 | C | THR | 22 | 134.192 | -3.629 | | 3.890 |
| ATOM | 198 | O | THR | 22 | 135.285 | -3.771 | | 4.487 |
| ATOM | 199 | CB | THR | 22 | 133.503 | -6.007 | | 4.667 |
| ATOM | 200 | OG1 | THR | 22 | 134.546 | -6.947 | | 4.452 |
| ATOM | 201 | HOG1 | THR | 22 | 135.012 | -6.623 | | 3.653 |
| ATOM | 202 | CG2 | THR | 22 | 132.165 | -6.722 | | 4.907 |
| ATOM | 203 | N | PRO | 23 | 133.769 | 2.399 | | 3.514 |
| ATOM | 204 | CA | PRO | 23 | 134.593 | -1.332 | | 3.113 |
| ATOM | 205 | C | PRO | 23 | 135.732 | -0.944 | | 3.972 |
| ATOM | 206 | O | PRO | 23 | 135.585 | -0.247 | | 5.015 |
| ATOM | 207 | CB | PRO | 23 | 133.700 | -0.181 | | 2.627 |
| ATOM | 208 | CG | PRO | 23 | 132.313 | -0.811 | | 2.548 |
| ATOM | 209 | CD | PRO | 23 | 132.421 | 2.037 | | 3.455 |
| ATOM | 210 | N | SER | 24 | 136.902 | -1.401 | | 3.551 |
| ATOM | 211 | HN | SER | 24 | 136.913 | -1.705 | | 2.662 |
| ATOM | 212 | CA | SER | 24 | 135.078 | 1.473 | | 4.295 |
| ATOM | 213 | C | SER | 24 | 139.055 | 0.462 | | 3.856 |
| ATOM | 214 | O | SER | 24 | 139.760 | -0.548 | | 2.819 |
| ATOM | 215 | CB | SER | 24 | 135.546 | 2.941 | | 4.338 |
| ATOM | 216 | OG | SER | 24 | 139.344 | -3.226 | | 5.480 |
| ATOM | 217 | HOG | SER | 24 | 140.275 | 2.389 | | 5.287 |
| ATOM | 218 | N | ALA | 25 | 139.136 | 0.634 | | 4.605 |
| ATOM | 219 | HN | ALA | 25 | 138.565 | 0.671 | | 5.353 |
| ATOM | 220 | CA | ALA | 25 | 139.980 | 1.735 | | 4.397 |
| ATOM | 221 | C | ALA | 25 | 141.412 | 1.429 | | 4.639 |
| ATOM | 222 | O | ALA | 25 | 141.761 | 0.836 | | 5.690 |
| ATOM | 223 | CB | ALA | 25 | 139.451 | 2.961 | | 5.156 |
| ATOM | 224 | N | LYS | 26 | 142.447 | 1.588 | | 3.846 |
| ATOM | 225 | HN | LYS | 26 | 143.189 | 1.166 | | 4.085 |
| ATOM | 226 | CA | LYS | 26 | 142.617 | 2.564 | | 2.755 |
| ATOM | 227 | C | LYS | 26 | 143.994 | 2.592 | | 2.175 |
| ATOM | 228 | O | LYS | 26 | 144.755 | 1.585 | | 2.226 |
| ATOM | 229 | CB | LYS | 26 | 141.479 | 2.526 | | 1.690 |
| ATOM | 230 | CG | LYS | 26 | 141.699 | 1.804 | | 0.343 |
| ATOM | 231 | CD | LYS | 26 | 141.577 | 0.275 | | 0.407 |
| ATOM | 232 | CE | LYS | 26 | 142.849 | 0.423 | | 0.901 |
| ATOM | 233 | NZ | LYS | 26 | 142.572 | 1.187 | | 2.116 |
| ATOM | 234 | HNZ1 | LYS | 26 | 143.161 | 0.689 | | 2.894 |
| ATOM | 235 | HNZ2 | LYS | 26 | 142.811 | 2.144 | | 1.860 |
| ATOM | 236 | HNZ3 | LYS | 26 | 141.589 | 1.079 | | 2.364 |
| ATOM | 237 | N | TYR | 27 | 144.383 | 3.723 | | 1.582 |
| ATOM | 238 | HN | TYR | 27 | 143.807 | 4.489 | | 1.806 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ATOM | 239 | CA | TYR | 27 | 145.424 | 3.914 | 0.651 |
| ATOM | 240 | C | TYR | 27 | 145.539 | 2.643 | -0.377 |
| ATOM | 241 | O | TYR | 27 | 144.584 | 2.778 | -1.194 |
| ATOM | 242 | CB | TYR | 27 | 146.716 | 4.466 | 1.294 |
| ATOM | 243 | CG | TYR | 27 | 146.658 | 5.870 | 1.720 |
| ATOM | 244 | CD1 | TYR | 27 | 146.711 | 6.147 | 3.109 |
| ATOM | 245 | CD2 | TYR | 27 | 146.656 | 6.912 | 0.763 |
| ATOM | 246 | CE1 | TYR | 27 | 146.676 | 7.487 | 3.551 |
| ATOM | 247 | CE2 | TYR | 27 | 146.521 | 8.254 | 1.201 |
| ATOM | 248 | CZ | TYR | 27 | 146.586 | 8.523 | 2.589 |
| ATOM | 249 | OH | TYR | 27 | 146.583 | 9.805 | 3.007 |
| ATOM | 250 | HOH | TYR | 27 | 146.502 | 10.533 | 2.353 |
| ATOM | 251 | N | CYS | 28 | 146.569 | 1.997 | -0.436 |
| ATOM | 252 | HN | CYS | 28 | 147.335 | 2.232 | 0.057 |
| ATOM | 253 | CA | CYS | 28 | 146.621 | 0.785 | -1.141 |
| ATOM | 254 | C | CYS | 28 | 146.545 | -0.467 | -0.328 |
| ATOM | 255 | O | CYS | 28 | 146.570 | -1.589 | -0.893 |
| ATOM | 256 | CB | CYS | 28 | 147.780 | 0.882 | -2.157 |
| ATOM | 257 | SG | CYS | 28 | 149.356 | 0.252 | -1.533 |
| ATOM | 258 | N | GLN | 29 | 146.445 | -0.446 | 0.994 |
| ATOM | 259 | HN | GLN | 29 | 145.835 | 0.253 | 1.364 |
| ATOM | 260 | CA | GLN | 29 | 147.012 | -1.321 | 1.930 |
| ATOM | 261 | C | GLN | 29 | 147.597 | -0.543 | 3.057 |
| ATOM | 262 | O | GLN | 29 | 148.735 | -0.869 | 3.471 |
| ATOM | 263 | CB | GLN | 29 | 146.026 | -2.422 | 2.361 |
| ATOM | 264 | CG | GLN | 29 | 145.995 | -3.704 | 1.514 |
| ATOM | 265 | CD | GLN | 29 | 144.673 | -4.326 | 1.285 |
| ATOM | 266 | OE1 | GLN | 29 | 143.661 | -3.659 | 0.968 |
| ATOM | 267 | NE2 | GLN | 29 | 144.454 | -5.612 | 1.386 |
| ATOM | 268 | HNE1 | GLN | 29 | 145.114 | -6.231 | 1.638 |
| ATOM | 269 | HNE2 | GLN | 29 | 143.588 | -5.927 | 1.200 |
| ATOM | 270 | N | VAL | 30 | 146.950 | 0.481 | 3.623 |
| ATOM | 271 | HN | VAL | 30 | 146.194 | 0.778 | 3.152 |
| ATOM | 272 | CA | VAL | 30 | 147.169 | 1.211 | 4.788 |
| ATOM | 273 | C | VAL | 30 | 147.568 | 0.493 | 6.019 |
| ATOM | 274 | O | VAL | 30 | 148.774 | 0.398 | 6.335 |
| ATOM | 275 | CB | VAL | 30 | 147.331 | 2.731 | 4.581 |
| ATOM | 276 | CG1 | VAL | 30 | 145.544 | 3.551 | 5.610 |
| ATOM | 277 | CG2 | VAL | 30 | 148.761 | 3.258 | 4.437 |
| ATOM | 278 | N | VAL | 31 | 146.690 | -0.078 | 6.835 |
| ATOM | 279 | HN | VAL | 31 | 147.035 | -0.549 | 7.570 |
| ATOM | 280 | CA | VAL | 31 | 145.295 | -0.039 | 6.703 |
| ATOM | 281 | C | VAL | 31 | 144.733 | -0.991 | 5.709 |
| ATOM | 282 | O | VAL | 31 | 144.249 | -0.507 | 4.641 |
| ATOM | 283 | CB | VAL | 31 | 144.656 | 0.185 | 8.096 |
| ATOM | 284 | CG1 | VAL | 31 | 143.910 | -0.962 | 8.797 |
| ATOM | 285 | CG2 | VAL | 31 | 143.806 | 1.457 | 8.135 |
| ATOM | 286 | N | CYS | 32 | 144.767 | -2.300 | 5.964 |
| ATOM | 287 | HN | CYS | 32 | 145.169 | -2.558 | 6.773 |
| ATOM | 288 | CA | CYS | 32 | 144.278 | -3.338 | 5.170 |
| ATOM | 289 | C | CYS | 32 | 142.800 | -3.479 | 5.329 |
| ATOM | 290 | O | CYS | 32 | 142.084 | -2.558 | 4.978 |
| ATOM | 291 | CB | CYS | 32 | 145.170 | -4.601 | 5.274 |
| ATOM | 292 | SG | CYS | 32 | 146.944 | -4.469 | 5.153 |
| ATOM | 293 | N | THR | 33 | 142.019 | -4.408 | 5.866 |
| ATOM | 294 | HN | THR | 33 | 141.117 | -4.151 | 5.856 |
| ATOM | 295 | CA | THR | 33 | 142.344 | -5.653 | 6.401 |
| ATOM | 296 | C | THR | 33 | 141.269 | -6.670 | 6.263 |
| ATOM | 297 | O | THR | 33 | 140.400 | -6.800 | 7.157 |
| ATOM | 298 | CB | THR | 33 | 143.242 | -5.664 | 7.662 |

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|---|---|---|---|---|---|---|---|
| ATOM | 299 | OG1 | THR | 33 | 144.004 | -6.865 | 7.680 |
| ATOM | 300 | HOG1 | THR | 33 | 144.062 | -7.186 | 6.757 |
| ATOM | 301 | CG2 | THR | 33 | 142.611 | -5.360 | 9.031 |
| ATOM | 302 | N | TYR | 34 | 141.107 | -7.604 | 5.239 |
| ATOM | 303 | HN | TYR | 34 | 140.427 | -8.144 | 5.346 |
| ATOM | 304 | CA | TYR | 34 | 141.788 | -7.562 | 4.021 |
| ATOM | 305 | C | TYR | 34 | 143.201 | -8.032 | 3.980 |
| ATOM | 306 | O | TYR | 34 | 144.022 | -7.724 | 4.890 |
| ATOM | 307 | CB | TYR | 34 | 141.419 | -6.419 | 3.055 |
| ATOM | 308 | CG | TYR | 34 | 140.533 | -6.887 | 1.981 |
| ATOM | 309 | CD1 | TYR | 34 | 141.091 | -7.241 | 0.727 |
| ATOM | 310 | CD2 | TYR | 34 | 139.136 | -6.978 | 2.209 |
| ATOM | 311 | CE1 | TYR | 34 | 140.249 | -7.700 | -0.315 |
| ATOM | 312 | CE2 | TYR | 34 | 138.283 | -7.443 | 1.175 |
| ATOM | 313 | CZ | TYR | 34 | 138.858 | -7.802 | -0.078 |
| ATOM | 314 | OH | TYR | 34 | 138.023 | -8.248 | -1.035 |
| ATOM | 315 | HOH | TYR | 34 | 138.315 | -8.497 | -1.936 |
| ATOM | 316 | N | HIS | 35 | 143.532 | -8.793 | 2.935 |
| ATOM | 317 | HN | HIS | 35 | 142.866 | -8.880 | 2.276 |
| ATOM | 318 | CA | HIS | 35 | 144.721 | -9.486 | 2.677 |
| ATOM | 319 | C | HIS | 35 | 146.027 | -8.793 | 2.862 |
| ATOM | 320 | O | HIS | 35 | 146.259 | -7.775 | 2.137 |
| ATOM | 321 | CB | HIS | 35 | 144.592 | -10.326 | 1.393 |
| ATOM | 322 | CG | HIS | 35 | 144.947 | -11.737 | 1.596 |
| ATOM | 323 | ND1 | HIS | 35 | 145.837 | -12.411 | 0.919 |
| ATOM | 324 | HND1 | HIS | 35 | 146.347 | -12.086 | 0.200 |
| ATOM | 325 | CD2 | HIS | 35 | 144.415 | -12.618 | 2.533 |
| ATOM | 326 | CE1 | HIS | 35 | 145.915 | -13.633 | 1.388 |
| ATOM | 327 | NE2 | HIS | 35 | 145.046 | -13.756 | 2.366 |
| ATOM | 328 | N | PRO | 36 | 146.932 | -9.215 | 3.771 |
| ATOM | 329 | CA | PRO | 36 | 147.939 | -8.415 | 4.323 |
| ATOM | 330 | C | PRO | 36 | 149.034 | -7.931 | 3.464 |
| ATOM | 331 | O | PRO | 36 | 149.762 | -8.716 | 2.794 |
| ATOM | 332 | CB | PRO | 36 | 148.434 | -9.108 | 5.602 |
| ATOM | 333 | CG | PRO | 36 | 147.547 | -10.345 | 5.725 |
| ATOM | 334 | CD | PRO | 36 | 146.989 | -10.501 | 4.311 |
| ATOM | 335 | N | ARG | 37 | 149.166 | -6.613 | 3.479 |
| ATOM | 336 | HN | ARG | 37 | 148.440 | -6.137 | 3.837 |
| ATOM | 337 | CA | ARG | 37 | 150.237 | -5.809 | 3.064 |
| ATOM | 338 | C | ARG | 37 | 149.997 | -4.450 | 3.508 |
| ATOM | 339 | O | ARG | 37 | 149.432 | -3.571 | 2.880 |
| ATOM | 340 | CB | ARG | 37 | 150.786 | -5.946 | 1.621 |
| ATOM | 341 | CG | ARG | 37 | 149.966 | -5.351 | 0.459 |
| ATOM | 342 | CD | ARG | 37 | 148.708 | -6.152 | 0.112 |
| ATOM | 343 | NE | ARG | 37 | 149.045 | -7.173 | -0.769 |
| ATOM | 344 | HNE | ARG | 37 | 149.725 | -6.966 | -1.385 |
| ATOM | 345 | CZ | ARG | 37 | 148.543 | -8.395 | -0.870 |
| ATOM | 346 | NH1 | ARG | 37 | 147.608 | -8.995 | -0.163 |
| ATOM | 347 | HN11 | ARG | 37 | 147.398 | -9.868 | -0.440 |
| ATOM | 348 | HN12 | ARG | 37 | 147.177 | -8.584 | 0.565 |
| ATOM | 349 | NH2 | ARG | 37 | 149.035 | -9.147 | -1.813 |
| ATOM | 350 | HN21 | ARG | 37 | 149.778 | -8.884 | -2.326 |
| ATOM | 351 | HN22 | ARG | 37 | 148.599 | -9.963 | -1.953 |
| ATOM | 352 | N | CYS | 38 | 150.393 | -4.224 | 4.835 |
| ATOM | 353 | HN | CYS | 38 | 150.923 | -4.883 | 5.247 |
| ATOM | 354 | CA | CYS | 38 | 150.079 | -3.097 | 5.590 |
| ATOM | 355 | C | CYS | 38 | 151.246 | -2.207 | 5.686 |
| ATOM | 356 | O | CYS | 38 | 152.178 | -2.400 | 6.527 |
| ATOM | 357 | CB | CYS | 38 | 149.393 | -3.552 | 6.891 |
| ATOM | 358 | SG | CYS | 38 | 147.617 | -3.578 | 6.826 |

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|---|---|---|---|---|---|---|---|---|
| ATOM | 359 | N | LEU | 39 | 151.255 | -1.204 | -4.818 |
| ATOM | 360 | HN | LEU | 39 | 150.464 | -1.083 | -4.325 |
| ATOM | 361 | CA | LEU | 39 | 152.319 | -0.330 | -4.580 |
| ATOM | 362 | C | LEU | 39 | 151.856 | 1.092 | -4.691 |
| ATOM | 363 | O | LEU | 39 | 151.591 | 1.759 | -3.681 |
| ATOM | 364 | CB | LEU | 39 | 153.273 | -0.752 | -3.436 |
| ATOM | 365 | CG | LEU | 39 | 152.680 | -0.861 | -2.024 |
| ATOM | 366 | CD1 | LEU | 39 | 153.605 | -0.150 | -1.034 |
| ATOM | 367 | CD2 | LEU | 39 | 152.597 | -2.339 | -1.629 |
| ATOM | 368 | N | LEU | 40 | 152.046 | 1.600 | -5.919 |
| ATOM | 369 | HN | LEU | 40 | 152.331 | 1.012 | -6.595 |
| ATOM | 370 | CA | LEU | 40 | 151.767 | 2.911 | -6.306 |
| ATOM | 371 | C | LEU | 40 | 152.931 | 3.806 | -6.131 |
| ATOM | 372 | O | LEU | 40 | 153.774 | 4.020 | -7.054 |
| ATOM | 373 | CB | LEU | 40 | 151.086 | 2.911 | -7.691 |
| ATOM | 374 | CG | LEU | 40 | 149.858 | 3.830 | -7.756 |
| ATOM | 375 | CD1 | LEU | 40 | 148.826 | 3.227 | -8.712 |
| ATOM | 376 | CD2 | LEU | 40 | 150.225 | 5.232 | -8.254 |
| ATOM | 377 | N | PHE | 41 | 153.022 | 4.354 | -4.924 |
| ATOM | 378 | HN | PHE | 41 | 152.346 | 4.122 | -4.314 |
| ATOM | 379 | CA | PHE | 41 | 154.016 | 5.221 | -4.479 |
| ATOM | 380 | C | PHE | 41 | 153.574 | 5.447 | -3.791 |
| ATOM | 381 | O | PHE | 41 | 154.021 | 7.504 | -4.314 |
| ATOM | 382 | CB | PHE | 41 | 155.177 | 4.479 | -3.782 |
| ATOM | 383 | CG | PHE | 41 | 156.455 | 5.131 | -4.084 |
| ATOM | 384 | CD1 | PHE | 41 | 157.107 | 4.876 | -5.321 |
| ATOM | 385 | CD2 | PHE | 41 | 157.028 | 6.018 | -3.134 |
| ATOM | 386 | CE1 | PHE | 41 | 158.308 | 5.562 | -5.633 |
| ATOM | 387 | CE2 | PHE | 41 | 158.235 | 6.692 | -3.441 |
| ATOM | 388 | CZ | PHE | 41 | 158.859 | 6.469 | -4.693 |
| ATOM | 389 | N | THR | 42 | 152.765 | 6.443 | -2.712 |
| ATOM | 390 | HN | THR | 42 | 152.440 | 5.615 | -2.430 |
| ATOM | 391 | CA | THR | 42 | 152.439 | 7.574 | -1.961 |
| ATOM | 392 | C | THR | 42 | 152.564 | 7.395 | -0.489 |
| ATOM | 393 | O | THR | 42 | 151.550 | 7.260 | -0.257 |
| ATOM | 394 | CB | THR | 42 | 151.232 | 8.331 | -2.575 |
| ATOM | 395 | OG1 | THR | 42 | 150.000 | 7.925 | -1.999 |
| ATOM | 396 | HOG1 | THR | 42 | 150.310 | 7.654 | -1.112 |
| ATOM | 397 | CG2 | THR | 42 | 151.397 | 9.847 | -2.407 |
| ATOM | 398 | N | PHE | 43 | 153.796 | 7.333 | -0.012 |
| ATOM | 399 | HN | PHE | 43 | 154.504 | 7.468 | -0.601 |
| ATOM | 400 | CA | PHE | 43 | 154.140 | 7.258 | -1.364 |
| ATOM | 401 | C | PHE | 43 | 153.727 | 8.396 | -2.212 |
| ATOM | 402 | O | PHE | 43 | 153.945 | 9.592 | -1.854 |
| ATOM | 403 | CB | PHE | 43 | 155.634 | 6.913 | -1.546 |
| ATOM | 404 | CG | PHE | 43 | 156.030 | 5.524 | -1.278 |
| ATOM | 405 | CD1 | PHE | 43 | 157.152 | 5.310 | -0.437 |
| ATOM | 406 | CD2 | PHE | 43 | 155.334 | 4.415 | -1.837 |
| ATOM | 407 | CE1 | PHE | 43 | 157.592 | 3.993 | -0.161 |
| ATOM | 408 | CE2 | PHE | 43 | 155.759 | 3.095 | -1.548 |
| ATOM | 409 | CZ | PHE | 43 | 156.691 | 2.895 | -0.719 |
| ATOM | 410 | N | THR | 44 | 153.128 | 8.067 | -3.357 |
| ATOM | 411 | HN | THR | 44 | 152.802 | 7.195 | -3.517 |
| ATOM | 412 | CA | THR | 44 | 152.644 | 8.992 | -4.382 |
| ATOM | 413 | C | THR | 44 | 153.966 | 9.036 | -5.344 |
| ATOM | 414 | O | THR | 44 | 154.299 | 8.004 | -5.984 |
| ATOM | 415 | CB | THR | 44 | 151.384 | 8.915 | -4.882 |
| ATOM | 416 | OG1 | THR | 44 | 151.103 | 7.905 | -5.840 |

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|---|---|---|---|---|---|---|---|---|
| ATOM | 418 | N | ALA | 45 | 154.567 | 10.204 | -5.467 |
| ATOM | 420 | HN | ALA | 46 | 154.164 | 10.931 | -5.027 |
| ATOM | 421 | CA | ALA | 45 | 155.771 | 10.470 | -6.165 |
| ATOM | 422 | C | ALA | 45 | 155.820 | 10.094 | -7.693 |
| ATOM | 423 | O | ALA | 45 | 154.937 | 10.524 | -8.393 |
| ATOM | 424 | CB | ALA | 45 | 156.248 | 11.899 | -5.863 |
| ATOM | 425 | N | GLU | 46 | 156.834 | 9.291 | -7.931 |
| ATOM | 426 | HN | GLU | 46 | 157.453 | 9.146 | -7.239 |
| ATOM | 427 | CA | GLU | 46 | 157.146 | 8.613 | -9.127 |
| ATOM | 428 | C | GLU | 46 | 158.577 | 8.235 | -9.131 |
| ATOM | 429 | O | GLU | 46 | 159.456 | 9.051 | -9.549 |
| ATOM | 430 | CB | GLU | 46 | 156.623 | 8.178 | -10.476 |
| ATOM | 431 | CG | GLU | 46 | 156.885 | 8.337 | -11.742 |
| ATOM | 432 | CD | GLU | 46 | 156.366 | 6.969 | -11.737 |
| ATOM | 433 | OE1 | GLU | 46 | 155.140 | 6.733 | -11.681 |
| ATOM | 434 | OE2 | GLU | 46 | 157.164 | 5.998 | -11.798 |
| ATOM | 435 | N | SER | 47 | 158.890 | 7.021 | -8.677 |
| ATOM | 436 | HN | SER | 47 | 158.209 | 6.512 | -8.176 |
| ATOM | 437 | CA | SER | 47 | 160.165 | 6.449 | -8.737 |
| ATOM | 438 | C | SER | 47 | 160.330 | 5.249 | -9.599 |
| ATOM | 439 | O | SER | 47 | 159.936 | 4.135 | -9.132 |
| ATOM | 440 | CB | SER | 47 | 160.898 | 6.392 | -7.384 |
| ATOM | 441 | OG | SER | 47 | 161.224 | 7.685 | -6.885 |
| ATOM | 442 | HOG | SER | 47 | 160.413 | 8.085 | -6.509 |
| ATOM | 443 | N | PRO | 48 | 160.886 | 5.331 | -10.330 |
| ATOM | 444 | CA | PRO | 48 | 161.565 | 4.202 | -11.464 |
| ATOM | 445 | C | PRO | 48 | 160.799 | 3.147 | -12.022 |
| ATOM | 446 | O | PRO | 48 | 160.005 | 3.296 | -12.990 |
| ATOM | 447 | CB | PRO | 48 | 162.535 | 4.926 | -12.465 |
| ATOM | 448 | CG | PRO | 48 | 162.016 | 6.352 | -12.640 |
| ATOM | 449 | CD | PRO | 48 | 160.873 | 6.479 | -11.629 |
| ATOM | 450 | N | SER | 49 | 161.043 | 1.992 | -11.417 |
| ATOM | 451 | HN | SER | 49 | 161.528 | 2.057 | -10.516 |
| ATOM | 452 | CA | SER | 49 | 160.736 | 0.657 | -11.716 |
| ATOM | 453 | C | SER | 49 | 161.964 | -0.158 | -11.593 |
| ATOM | 454 | O | SER | 49 | 162.263 | -0.471 | -10.411 |
| ATOM | 455 | CB | SER | 49 | 159.740 | 0.277 | -12.835 |
| ATOM | 456 | OG | SER | 49 | 158.504 | -0.129 | -12.269 |
| ATOM | 457 | HOG | SER | 49 | 159.215 | 0.555 | -11.629 |
| ATOM | 458 | N | GLU | 50 | 162.706 | -0.530 | -12.639 |
| ATOM | 459 | HN | GLU | 50 | 162.420 | -0.248 | -13.489 |
| ATOM | 460 | CA | GLU | 50 | 163.871 | -1.306 | -12.593 |
| ATOM | 461 | C | GLU | 50 | 165.162 | -0.551 | -12.744 |
| ATOM | 462 | O | GLU | 50 | 165.327 | 0.267 | -13.658 |
| ATOM | 463 | CB | GLU | 50 | 163.732 | -2.548 | -13.490 |
| ATOM | 464 | CG | GLU | 50 | 164.418 | -3.740 | -12.805 |
| ATOM | 465 | CD | GLU | 50 | 163.753 | -5.038 | -12.931 |
| ATOM | 466 | OE1 | GLU | 50 | 162.591 | -5.256 | -12.535 |
| ATOM | 467 | OE2 | GLU | 50 | 164.366 | -5.996 | -13.434 |
| ATOM | 468 | N | ASP | 51 | 166.226 | -0.752 | -11.962 |
| ATOM | 469 | HN | ASP | 51 | 166.986 | -0.234 | -12.151 |
| ATOM | 470 | CA | ASP | 51 | 166.310 | -1.635 | -10.885 |
| ATOM | 471 | C | ASP | 51 | 165.928 | -1.071 | -9.571 |
| ATOM | 472 | O | ASP | 51 | 164.815 | -1.545 | -9.238 |
| ATOM | 473 | CB | ASP | 51 | 167.607 | -2.474 | -10.847 |
| ATOM | 474 | CG | ASP | 51 | 167.487 | -3.796 | -10.209 |
| ATOM | 475 | OD1 | ASP | 51 | 166.830 | -4.016 | -9.163 |
| ATOM | 476 | OD2 | ASP | 51 | 168.062 | -4.734 | -10.705 |
| ATOM | 477 | N | PRO | 52 | 166.614 | -0.196 | -8.794 |
| ATOM | 478 | CA | PRO | 52 | 166.508 | -0.083 | -7.392 |

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|---|---|---|---|---|---|---|---|
| ATOM | 479 | C | PRO | 52 | 165.352 | 0.618 | -6.752 |
| ATOM | 480 | O | PRO | 52 | 165.448 | 1.512 | -5.065 |
| ATOM | 481 | CB | PRO | 52 | 167.919 | 0.332 | -6.945 |
| ATOM | 482 | CG | PRO | 52 | 168.592 | 0.900 | -8.193 |
| ATOM | 483 | CD | PRO | 52 | 167.553 | 0.702 | -9.296 |
| ATOM | 484 | N | THR | 53 | 164.176 | 0.216 | -7.187 |
| ATOM | 485 | HN | THR | 53 | 164.269 | -0.383 | -7.905 |
| ATOM | 486 | CA | THR | 53 | 162.873 | 0.505 | -6.777 |
| ATOM | 487 | C | THR | 53 | 162.120 | -0.765 | -6.685 |
| ATOM | 488 | O | THR | 53 | 161.903 | -1.183 | -5.513 |
| ATOM | 489 | CB | THR | 53 | 162.141 | 1.680 | -7.481 |
| ATOM | 490 | OG1 | THR | 53 | 162.479 | 1.944 | -8.845 |
| ATOM | 491 | HOG1 | THR | 53 | 162.400 | 1.124 | -9.375 |
| ATOM | 492 | CG2 | THR | 53 | 162.307 | 2.981 | -6.685 |
| ATOM | 493 | N | ARG | 54 | 161.717 | -1.415 | -7.780 |
| ATOM | 494 | HN | ARG | 54 | 161.919 | -1.024 | -8.610 |
| ATOM | 495 | CA | ARG | 54 | 161.021 | -2.626 | -7.809 |
| ATOM | 496 | C | ARG | 54 | 159.542 | -2.502 | -7.912 |
| ATOM | 497 | O | ARG | 54 | 158.964 | -1.455 | -8.306 |
| ATOM | 498 | CB | ARG | 54 | 161.509 | -3.413 | -9.132 |
| ATOM | 499 | CG | ARG | 54 | 162.917 | -4.016 | -9.027 |
| ATOM | 500 | CD | ARG | 54 | 162.942 | -5.547 | -9.016 |
| ATOM | 501 | NE | ARG | 54 | 163.846 | -5.970 | -9.966 |
| ATOM | 502 | HNE | ARG | 54 | 163.561 | -5.793 | -10.863 |
| ATOM | 503 | CZ | ARG | 54 | 165.028 | -6.572 | -9.858 |
| ATOM | 504 | NH1 | ARG | 54 | 165.641 | -7.004 | -8.771 |
| ATOM | 505 | HN11 | ARG | 54 | 166.526 | -7.314 | -8.833 |
| ATOM | 506 | HN12 | ARG | 54 | 165.202 | -7.011 | -7.940 |
| ATOM | 507 | NH2 | ARG | 54 | 165.680 | -6.760 | -10.974 |
| ATOM | 508 | HN21 | ARG | 54 | 166.528 | -7.187 | -10.965 |
| ATOM | 509 | HN22 | ARG | 54 | 165.281 | -6.519 | -11.784 |
| ATOM | 510 | N | TRP | 55 | 158.851 | -3.555 | -7.494 |
| ATOM | 511 | HN | TRP | 55 | 159.382 | -4.310 | -7.317 |
| ATOM | 512 | CA | TRP | 55 | 157.478 | -3.743 | -7.261 |
| ATOM | 513 | C | TRP | 55 | 156.466 | -3.115 | -8.155 |
| ATOM | 514 | O | TRP | 55 | 156.280 | -3.712 | -9.241 |
| ATOM | 515 | CB | TRP | 55 | 157.074 | -4.016 | -5.768 |
| ATOM | 516 | CG | TRP | 55 | 158.068 | -3.723 | -4.740 |
| ATOM | 517 | CD1 | TRP | 55 | 159.068 | -4.606 | -4.395 |
| ATOM | 518 | CD2 | TRP | 55 | 158.231 | -2.565 | -3.969 |
| ATOM | 519 | NE1 | TRP | 55 | 159.831 | -3.906 | -3.450 |
| ATOM | 520 | HNE1 | TRP | 55 | 160.582 | -4.378 | -3.041 |
| ATOM | 521 | CE2 | TRP | 55 | 159.395 | -2.768 | -3.239 |
| ATOM | 522 | CE3 | TRP | 55 | 157.484 | -1.368 | -3.866 |
| ATOM | 523 | CZ2 | TRP | 55 | 159.922 | -1.753 | -2.413 |
| ATOM | 524 | CZ3 | TRP | 55 | 157.981 | -0.361 | -3.022 |
| ATOM | 525 | CH2 | TRP | 55 | 159.196 | -0.540 | -2.312 |
| ATOM | 526 | N | PHE | 56 | 155.735 | -2.016 | -7.972 |
| ATOM | 527 | HN | PHE | 56 | 155.092 | -1.810 | -8.625 |
| ATOM | 528 | CA | PHE | 56 | 155.830 | -1.139 | -6.890 |
| ATOM | 529 | C | PHE | 56 | 154.634 | -1.168 | -6.014 |
| ATOM | 530 | O | PHE | 56 | 154.605 | -2.128 | -5.210 |
| ATOM | 531 | CB | PHE | 56 | 156.355 | 0.216 | -7.402 |
| ATOM | 532 | CG | PHE | 56 | 157.068 | 1.044 | -6.423 |
| ATOM | 533 | CD1 | PHE | 56 | 156.350 | 1.765 | -5.447 |
| ATOM | 534 | CD2 | PHE | 56 | 158.485 | 1.104 | -6.455 |
| ATOM | 535 | CE1 | PHE | 56 | 157.049 | 2.595 | -4.522 |
| ATOM | 536 | CE2 | PHE | 56 | 159.186 | 1.913 | -5.539 |
| ATOM | 537 | CZ | PHE | 56 | 158.463 | 2.658 | -4.578 |
| ATOM | 538 | N | THR | 57 | 153.645 | -0.269 | -6.033 |

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|---|---|---|---|---|---|---|---|---|
| ATOM | 539 | HN | THR | 57 | 153.776 | 0.499 | -6.556 |
| ATOM | 540 | CA | THR | 57 | 152.406 | -0.308 | -5.359 |
| ATOM | 541 | C | THR | 57 | 152.501 | 0.032 | -3.912 |
| ATOM | 542 | O | THR | 57 | 152.636 | 1.241 | -3.603 |
| ATOM | 543 | CB | THR | 57 | 151.360 | -1.364 | -5.823 |
| ATOM | 544 | OG1 | THR | 57 | 151.850 | -2.704 | -5.814 |
| ATOM | 545 | HOG1 | THR | 57 | 152.803 | -2.518 | -5.611 |
| ATOM | 546 | CG2 | THR | 57 | 150.763 | -1.072 | -7.208 |
| ATOM | 547 | N | CYS | 58 | 152.469 | -0.756 | -2.844 |
| ATOM | 548 | HN | CYS | 58 | 152.713 | -0.355 | -2.030 |
| ATOM | 549 | CA | CYS | 58 | 152.106 | -2.105 | -2.762 |
| ATOM | 550 | C | CYS | 58 | 153.191 | -3.080 | -2.532 |
| ATOM | 551 | O | CYS | 58 | 153.999 | -2.880 | -1.581 |
| ATOM | 552 | CB | CYS | 58 | 150.955 | -2.295 | -1.773 |
| ATOM | 553 | SG | CYS | 58 | 149.409 | -1.635 | -2.332 |
| ATOM | 554 | N | VAL | 59 | 153.272 | -4.153 | -3.325 |
| ATOM | 555 | HN | VAL | 59 | 152.772 | -4.095 | -4.117 |
| ATOM | 556 | CA | VAL | 59 | 154.021 | -5.333 | -3.079 |
| ATOM | 557 | C | VAL | 59 | 154.544 | -6.131 | -4.219 |
| ATOM | 558 | O | VAL | 59 | 153.894 | -6.255 | -5.290 |
| ATOM | 559 | CB | VAL | 59 | 153.408 | -6.343 | -2.064 |
| ATOM | 560 | CG1 | VAL | 59 | 153.619 | -6.012 | -0.586 |
| ATOM | 561 | CG2 | VAL | 59 | 151.999 | -6.891 | -2.343 |
| ATOM | 562 | N | LEU | 60 | 155.728 | -6.725 | -4.001 |
| ATOM | 563 | HN | LEU | 60 | 156.246 | -6.374 | -3.329 |
| ATOM | 564 | CA | LEU | 60 | 156.301 | -7.611 | -4.717 |
| ATOM | 565 | C | LEU | 60 | 157.046 | -7.597 | -5.972 |
| ATOM | 566 | O | LEU | 60 | 156.476 | -7.150 | -6.998 |
| ATOM | 567 | CB | LEU | 60 | 155.451 | -9.099 | -4.715 |
| ATOM | 568 | CG | LEU | 60 | 155.883 | -10.058 | -3.609 |
| ATOM | 569 | CD1 | LEU | 60 | 154.768 | -10.176 | -2.556 |
| ATOM | 570 | CD2 | LEU | 60 | 156.161 | -11.436 | -4.204 |
| ATOM | 571 | N | LYS | 61 | 158.336 | -7.919 | -5.940 |
| ATOM | 572 | HN | LYS | 61 | 158.657 | -8.259 | -5.125 |
| ATOM | 573 | CA | LYS | 61 | 159.271 | -7.807 | -6.976 |
| ATOM | 574 | C | LYS | 61 | 160.421 | -8.998 | -6.518 |
| ATOM | 575 | O | LYS | 61 | 160.480 | -5.602 | -6.991 |
| ATOM | 576 | CB | LYS | 61 | 159.536 | -9.201 | -7.594 |
| ATOM | 577 | CG | LYS | 61 | 160.803 | -9.360 | -8.452 |
| ATOM | 578 | CD | LYS | 61 | 161.761 | -10.283 | -7.685 |
| ATOM | 579 | CE | LYS | 61 | 163.214 | -10.141 | -8.145 |
| ATOM | 580 | NZ | LYS | 61 | 164.075 | -10.101 | -6.963 |
| ATOM | 581 | HNZ1 | LYS | 61 | 164.146 | -9.131 | -6.656 |
| ATOM | 582 | HNZ2 | LYS | 61 | 165.002 | -10.453 | -7.202 |
| ATOM | 583 | HNZ3 | LYS | 61 | 163.670 | -10.671 | -6.224 |
| ATOM | 584 | N | ASP | 62 | 161.329 | -7.463 | -5.660 |
| ATOM | 585 | HN | ASP | 62 | 161.324 | -8.388 | -5.491 |
| ATOM | 586 | CA | ASP | 62 | 162.276 | -6.701 | -4.962 |
| ATOM | 587 | C | ASP | 62 | 163.557 | -6.402 | -5.655 |
| ATOM | 588 | O | ASP | 62 | 164.261 | -7.305 | -6.188 |
| ATOM | 589 | CB | ASP | 62 | 162.385 | -7.242 | -3.549 |
| ATOM | 590 | CG | ASP | 62 | 162.823 | -6.169 | -2.665 |
| ATOM | 591 | OD1 | ASP | 62 | 162.041 | -5.317 | -2.202 |
| ATOM | 592 | OD2 | ASP | 62 | 164.021 | -6.083 | -2.356 |
| ATOM | 593 | N | SER | 63 | 163.901 | -5.122 | -5.650 |
| ATOM | 594 | HN | SER | 63 | 163.280 | -4.535 | -5.246 |
| ATOM | 595 | CA | SER | 63 | 165.063 | -4.524 | -6.162 |
| ATOM | 596 | C | SER | 63 | 166.383 | -4.976 | -5.661 |
| ATOM | 597 | O | SER | 63 | 166.510 | -5.420 | -4.492 |
| ATOM | 598 | CB | SER | 63 | 164.929 | -2.965 | -6.200 |

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|---|---|---|---|---|---|---|---|
| ATOM | 599 | OG | SER | 63 | 164.546 | -2.318 | -4.999 |
| ATOM | 600 | HOG | SER | 63 | 163.659 | -1.927 | -5.141 |
| ATOM | 601 | N | VAL | 64 | 167.415 | -4.875 | -6.502 |
| ATOM | 602 | HN | VAL | 64 | 167.207 | -4.606 | -7.376 |
| ATOM | 603 | CA | VAL | 64 | 168.779 | -5.105 | -6.251 |
| ATOM | 604 | C | VAL | 64 | 169.333 | -4.466 | -5.032 |
| ATOM | 605 | O | VAL | 64 | 169.988 | -5.217 | -4.262 |
| ATOM | 606 | CB | VAL | 64 | 169.609 | -5.042 | -7.559 |
| ATOM | 607 | CG1 | VAL | 64 | 170.281 | -3.711 | -7.938 |
| ATOM | 608 | CG2 | VAL | 64 | 170.642 | -6.172 | -7.628 |
| ATOM | 609 | N | THR | 65 | 169.116 | -3.169 | -4.789 |
| ATOM | 610 | HN | THR | 65 | 168.818 | -2.645 | -5.510 |
| ATOM | 611 | CA | THR | 65 | 169.270 | -2.513 | -3.566 |
| ATOM | 612 | C | THR | 65 | 168.229 | -2.934 | -2.604 |
| ATOM | 613 | O | THR | 65 | 167.001 | -2.720 | -2.808 |
| ATOM | 614 | CB | THR | 65 | 169.555 | -1.009 | -3.763 |
| ATOM | 615 | OG1 | THR | 65 | 166.442 | -0.125 | -3.654 |
| ATOM | 616 | HOG1 | THR | 65 | 168.267 | 0.112 | -2.719 |
| ATOM | 617 | CG2 | THR | 65 | 170.691 | -0.543 | -2.847 |
| ATOM | 618 | N | GLU | 66 | 168.711 | -3.549 | -1.508 |
| ATOM | 619 | HN | GLU | 66 | 169.616 | -3.366 | -1.358 |
| ATOM | 620 | CA | GLU | 66 | 168.111 | -4.445 | -0.646 |
| ATOM | 621 | C | GLU | 66 | 166.698 | -4.417 | -0.197 |
| ATOM | 622 | O | GLU | 66 | 166.049 | -3.352 | -0.041 |
| ATOM | 623 | CB | GLU | 66 | 169.140 | -4.800 | 0.442 |
| ATOM | 624 | CG | GLU | 66 | 169.894 | -6.095 | 0.079 |
| ATOM | 625 | CD | GLU | 66 | 169.133 | -7.345 | 0.212 |
| ATOM | 626 | OE1 | GLU | 66 | 168.176 | -7.652 | -0.506 |
| ATOM | 627 | OE2 | GLU | 66 | 169.445 | -8.151 | 1.106 |
| ATOM | 628 | N | THR | 67 | 166.185 | -5.618 | 0.020 |
| ATOM | 629 | HN | THR | 67 | 166.612 | -6.302 | -0.126 |
| ATOM | 630 | CA | THR | 67 | 164.922 | -6.077 | 0.411 |
| ATOM | 631 | C | THR | 67 | 163.890 | -5.259 | 1.094 |
| ATOM | 632 | O | THR | 67 | 164.174 | -4.601 | 2.119 |
| ATOM | 633 | CB | THR | 67 | 165.150 | -7.522 | 0.902 |
| ATOM | 634 | OG1 | THR | 67 | 165.274 | -7.723 | 2.304 |
| ATOM | 635 | HOG1 | THR | 67 | 165.609 | -6.934 | 2.776 |
| ATOM | 636 | CG2 | THR | 67 | 164.131 | -8.517 | 0.333 |
| ATOM | 637 | N | LEU | 68 | 162.655 | -5.252 | 0.594 |
| ATOM | 638 | HN | LEU | 68 | 162.584 | -5.438 | 0.392 |
| ATOM | 639 | CA | LEU | 68 | 161.410 | -5.035 | 1.205 |
| ATOM | 640 | C | LEU | 68 | 160.682 | -3.750 | 0.882 |
| ATOM | 641 | O | LEU | 68 | 161.322 | -2.678 | 1.055 |
| ATOM | 642 | CB | LEU | 68 | 161.169 | -5.430 | 2.650 |
| ATOM | 643 | CG | LEU | 68 | 159.783 | -6.132 | 2.806 |
| ATOM | 644 | CD1 | LEU | 68 | 159.902 | -7.624 | 3.124 |
| ATOM | 645 | CD2 | LEU | 68 | 158.977 | -5.419 | 3.895 |
| ATOM | 646 | N | PRO | 69 | 159.407 | -3.723 | 0.402 |
| ATOM | 647 | CA | PRO | 69 | 158.548 | -2.605 | 0.371 |
| ATOM | 648 | C | PRO | 69 | 158.589 | -1.652 | 1.458 |
| ATOM | 649 | O | PRO | 69 | 158.385 | -2.050 | 2.682 |
| ATOM | 650 | CB | PRO | 69 | 157.131 | -3.031 | 0.037 |
| ATOM | 651 | CG | PRO | 69 | 157.376 | -4.426 | -0.654 |
| ATOM | 652 | CD | PRO | 69 | 158.758 | -4.837 | -0.144 |
| ATOM | 653 | N | ARG | 70 | 156.863 | -0.336 | 1.161 |
| ATOM | 654 | HN | ARG | 70 | 156.855 | -0.103 | 0.246 |
| ATOM | 655 | CA | ARG | 70 | 159.170 | 0.636 | 2.040 |
| ATOM | 656 | C | ARG | 70 | 158.077 | 1.109 | 2.909 |
| ATOM | 657 | O | ARG | 70 | 157.055 | 1.697 | 2.467 |
| ATOM | 658 | CB | ARG | 70 | 160.015 | 1.730 | 1.355 |

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|---|---|---|---|---|---|---|
| ATOM | 659 CG ARG | 70 | 161.102 | 2.271 | 2.256 |
| ATOM | 660 CD ARG | 70 | 160.640 | 3.576 | 2.956 |
| ATOM | 661 NE ARG | 70 | 160.851 | 3.570 | 4.336 |
| ATOM | 662 HNE ARG | 70 | 160.416 | 2.916 | 4.853 |
| ATOM | 663 CZ ARG | 70 | 161.592 | 4.377 | 5.090 |
| ATOM | 664 NH1 ARG | 70 | 162.327 | 5.415 | 4.731 |
| ATOM | 665 HN11 ARG | 70 | 162.349 | 5.675 | 3.828 |
| ATOM | 666 HN12 ARG | 70 | 162.822 | 5.869 | 5.374 |
| ATOM | 667 NH2 ARG | 70 | 161.559 | 4.068 | 6.360 |
| ATOM | 668 HN21 ARG | 70 | 162.059 | 4.537 | 7.004 |
| ATOM | 669 HN22 ARG | 70 | 160.958 | 3.348 | 6.581 |
| ATOM | 670 N VAL | 71 | 158.291 | 0.846 | 4.182 |
| ATOM | 671 HN VAL | 71 | 159.058 | 0.336 | 4.367 |
| ATOM | 672 CA VAL | 71 | 157.611 | 1.183 | 5.358 |
| ATOM | 673 C VAL | 71 | 158.619 | 1.114 | 6.464 |
| ATOM | 674 O VAL | 71 | 159.636 | 1.867 | 6.373 |
| ATOM | 675 CB VAL | 71 | 156.227 | 0.475 | 5.473 |
| ATOM | 676 CG1 VAL | 71 | 156.186 | -1.059 | 5.621 |
| ATOM | 677 CG2 VAL | 71 | 155.351 | 1.092 | 6.566 |
| ATOM | 678 N ASN | 72 | 158.501 | 0.299 | 7.518 |
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| ATOM | 680 CA ASN | 72 | 159.484 | 0.043 | 8.476 |
| ATOM | 681 C ASN | 72 | 159.682 | -1.388 | 8.790 |
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| ATOM | 683 CB ASN | 72 | 159.405 | 1.024 | 9.667 |
| ATOM | 684 CG ASN | 72 | 160.726 | 1.334 | 10.220 |
| ATOM | 685 OD1 ASN | 72 | 161.568 | 1.991 | 9.556 |
| ATOM | 686 ND2 ASN | 72 | 161.041 | 0.935 | 11.427 |
| ATOM | 687 HND1 ASN | 72 | 160.422 | 0.454 | 11.944 |
| ATOM | 688 HND2 ASN | 72 | 161.890 | 1.133 | 11.775 |
| ATOM | 689 N ARG | 73 | 160.557 | -2.032 | 8.024 |
| ATOM | 690 HN ARG | 73 | 160.851 | -1.579 | 7.255 |
| ATOM | 691 CA ARG | 73 | 161.068 | -2.315 | 8.256 |
| ATOM | 692 C ARG | 73 | 162.498 | -2.876 | 8.628 |
| ATOM | 693 O ARG | 73 | 163.383 | -2.802 | 7.936 |
| ATOM | 694 CB ARG | 73 | 160.696 | -4.255 | 7.103 |
| ATOM | 695 CG ARG | 73 | 160.647 | -5.729 | 7.575 |
| ATOM | 696 CD ARG | 73 | 161.211 | -6.698 | 6.527 |
| ATOM | 697 NE ARG | 73 | 162.600 | -6.833 | 6.609 |
| ATOM | 698 HNE ARG | 73 | 163.006 | -6.651 | 7.441 |
| ATOM | 699 CZ ARG | 73 | 163.489 | -7.154 | 5.675 |
| ATOM | 700 NH1 ARG | 73 | 164.681 | -7.156 | 6.204 |
| ATOM | 701 HN11 ARG | 73 | 165.477 | -7.412 | 5.763 |
| ATOM | 702 HN12 ARG | 73 | 164.700 | -6.959 | 7.116 |
| ATOM | 703 NH2 ARG | 73 | 163.286 | -7.411 | 4.401 |
| ATOM | 704 HN21 ARG | 73 | 162.403 | -7.450 | 4.060 |
| ATOM | 705 HN22 ARG | 73 | 163.992 | -7.554 | 3.798 |
| ATOM | 706 N THR | 74 | 162.767 | -4.032 | 9.721 |
| ATOM | 707 HN THR | 74 | 162.021 | -4.355 | 10.296 |
| ATOM | 708 CA THR | 74 | 164.022 | -4.439 | 10.235 |
| ATOM | 709 C THR | 74 | 164.820 | -5.345 | 9.378 |
| ATOM | 710 O THR | 74 | 164.320 | -6.433 | 8.960 |
| ATOM | 711 CB THR | 74 | 163.911 | -4.814 | 11.739 |
| ATOM | 712 OG1 THR | 74 | 165.126 | -4.547 | 12.422 |
| ATOM | 713 HOG1 THR | 74 | 165.879 | -4.645 | 11.803 |
| ATOM | 714 CG2 THR | 74 | 163.395 | -6.215 | 12.119 |
| ATOM | 715 N ALA | 75 | 166.055 | -4.971 | 9.077 |
| ATOM | 716 HN ALA | 75 | 166.341 | -4.146 | 9.427 |
| ATOM | 717 CA ALA | 75 | 166.995 | -5.668 | 8.295 |
| ATOM | 718 C ALA | 75 | 167.758 | -6.715 | 9.019 |

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| ATOM | 719 | O | ALA | 75 | 168.335 | -8.447 | 10.116 |
| ATOM | 720 | CB | ALA | 75 | 167.877 | -4.666 | 7.534 |
| ATOM | 721 | N | ALA | 76 | 167.807 | -7.937 | 8.475 |
| ATOM | 722 | HN | ALA | 76 | 167.513 | -7.996 | 7.585 |
| ATOM | 723 | CA | ALA | 76 | 168.256 | -9.131 | 9.077 |
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| ATOM | 725 | O | ALA | 76 | 167.504 | -10.777 | 7.511 |
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| ATOM | 729 | CA | ILE | 77 | 170.255 | -11.316 | 6.761 |
| ATOM | 730 | C | ILE | 77 | 170.114 | -10.636 | 5.440 |
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| ATOM | 734 | CG2 | ILE | 77 | 170.474 | -13.693 | 5.695 |
| ATOM | 735 | CD1 | ILE | 77 | 169.052 | -13.862 | 9.010 |
| ATOM | 736 | N | SER | 78 | 168.911 | -10.211 | 5.085 |
| ATOM | 737 | HN | SER | 78 | 168.269 | -10.448 | 5.726 |
| ATOM | 738 | CA | SER | 78 | 168.484 | -9.477 | 3.984 |
| ATOM | 739 | C | SER | 78 | 168.101 | -8.097 | 4.379 |
| ATOM | 740 | O | SER | 78 | 167.386 | -7.884 | 5.412 |
| ATOM | 741 | CB | SER | 78 | 167.487 | -10.298 | 3.139 |
| ATOM | 742 | OG | SER | 78 | 166.119 | -10.193 | 3.520 |
| ATOM | 743 | HOG | SER | 78 | 165.782 | -9.358 | 2.133 |
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| ATOM | 747 | C | GLY | 79 | 167.334 | -4.969 | 3.804 |
| ATOM | 748 | O | GLY | 79 | 166.209 | -5.533 | 3.902 |
| ATOM | 749 | N | TYR | 80 | 167.477 | -3.649 | 3.683 |
| ATOM | 750 | HN | TYR | 80 | 168.359 | -3.333 | 3.607 |
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| ATOM | 752 | C | TYR | 80 | 166.848 | -1.382 | 3.068 |
| ATOM | 753 | O | TYR | 80 | 167.383 | -0.472 | 3.774 |
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| ATOM | 756 | CD1 | TYR | 80 | 163.379 | -2.853 | 4.500 |
| ATOM | 757 | CD2 | TYR | 80 | 164.195 | -0.726 | 5.401 |
| ATOM | 758 | CE1 | TYR | 80 | 162.067 | -2.346 | 4.473 |
| ATOM | 759 | CE2 | TYR | 80 | 162.881 | -0.217 | 5.460 |
| ATOM | 760 | CZ | TYR | 80 | 161.842 | -1.050 | 4.984 |
| ATOM | 761 | OH | TYR | 80 | 160.576 | -0.618 | 5.019 |
| ATOM | 762 | HOH | TYR | 80 | 160.330 | 0.238 | 5.427 |
| ATOM | 763 | N | SER | 81 | 166.609 | -1.196 | 1.772 |
| ATOM | 764 | HN | SER | 81 | 166.356 | -1.942 | 1.256 |
| ATOM | 765 | CA | SER | 81 | 166.698 | 0.005 | 1.057 |
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| ATOM | 768 | CB | SER | 81 | 167.093 | -0.343 | -0.384 |
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| ATOM | 770 | HOG | SER | 81 | 168.094 | 0.397 | -1.504 |
| ATOM | 771 | N | PHE | 82 | 165.761 | 2.198 | 1.295 |
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| ATOM | 773 | CA | PHE | 82 | 164.828 | 3.230 | 1.408 |
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| ATOM | 776 | CB | PHE | 82 | 165.226 | 4.268 | 2.469 |
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| ATOM | 778 | CD1 | PHE | 82 | 164.872 | 3.097 | 4.660 |

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ATOM    781 CE2 PHE     82      167.623    3.474    5.282
ATOM    782 CZ  PHE     82      166.766    2.786    6.176
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ATOM    784 HN  LYS     83      163.666    1.955   -0.212
ATOM    785 CA  LYS     83      163.018    2.949   -1.360
ATOM    786 C   LYS     83      161.679    3.560   -1.861
ATOM    787 O   LYS     83      160.609    2.941   -2.059
ATOM    788 CB  LYS     83      163.302    1.793   -2.646
ATOM    789 CG  LYS     83      162.671    0.440   -2.469
ATOM    790 CD  LYS     83      163.767   -0.564   -2.185
ATOM    791 CE  LYS  83  163.143   -1.841   -1.578
ATOM    792 NZ  LYS  83  163.903   -3.000   -2.017
ATOM    793 HNZ1 LYS 83  164.682   -3.141   -1.375
ATOM    794 HNZ2 LYS 83  164.231   -2.810   -2.964
ATOM    795 HNZ3 LYS 83  163.312   -3.828   -2.039
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ATOM    798 CA  GLN  84  160.692    5.836   -1.763
ATOM    799 C   GLN  84  160.352    6.247   -3.144
ATOM    800 O   GLN  84  161.261    6.483   -3.993
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ATOM    805 NE2 GLN  84  161.713    8.352              2.065
ATOM    806 HNE1 GLN 84  161.160    9.065              1.817
ATOM    807 HNE2 GLN 84  162.379    8.489              2.731
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ATOM    809 HN  CYS  85  158.455    6.116   -2.732
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SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Temple University - Of The Commonwealth System of Higher Education

(ii) INVENTORS: Walsh, Peter N., Baglia, Frank A., Jameson, Bradford A.

(iii) TITLE OF INVENTION: PEPTIDE ANALOGS OF THE ACTIVATED PLATELET BINDING SITE ON FACTOR XI

(iv) NUMBER OF SEQUENCES: 23

(v) CORRESPONDENCE ADDRESS:

(A) ADDRESSEE: Seidel, Gonda, Lavorgna & Monaco, P.C.

(B) STREET: Two Penn Center Plaza, Suite 1800

(C) CITY: Philadelphia

(D) STATE: Pennsylvania

(E) COUNTRY: U.S.A.

(F) ZIP: 19102

(vi) COMPUTER READABLE FORM:

(A) MEDIUM TYPE: Diskette, 3.50 inch, 720 Kb

(B) COMPUTER: IBM PS/2

(C) OPERATING SYSTEM: MS-DOS

(D) SOFTWARE: WordPerfect 5.1

(vii) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:

(B) FILING DATE:

(C) CLASSIFICATION:

(viii) PRIOR APPLICATION DATA:

(A) APPLICATION NUMBER: 08/172,002

(B) FILING DATE: 22 December 1993

(ix) ATTORNEY/AGENT INFORMATION:

(A) NAME: Monaco, Daniel A.

(B) REGISTRATION NUMBER: 30,480

(C) REFERENCE/DOCKET NUMBER: 6056-194PC

(x) TELECOMMUNICATION INFORMATION:

(A) TELEPHONE: (215) 568-8383

(B) TELEFAX: (215)

(2) **INFORMATION FOR SEQ ID NO:1:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 86 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:1:**

Ala Cys Ile Arg Asp Ile Phe Pro Asn Thr Val Phe Ala Asp Ser
5 10 15

Asn Ile Asp Ser Val Met Ala Pro Asp Ala Phe Val Cys Gly Arg
20 25 30

Ile Cys Thr His His Pro Gly Cys Leu Phe Phe Thr Phe Phe Ser
35 40 45

Gln Glu Trp Pro Lys Glu Ser Gln Arg Asn Leu Cys Leu Leu Lys
50 55 60

Thr Ser Glu Ser Gly Leu Pro Ser Thr Arg Ile Lys Lys Ser Lys
65 70 75

Ala Leu Ser Gly Phe Ser Leu Gln Ser Cys Arg
80 85

(3) **INFORMATION FOR SEQ ID NO:2:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 32 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:2:**

Asn Leu Cys Leu Leu Lys Thr Ser Glu Ser Gly Leu Pro Ser Thr
5 10 15

Arg Ile Lys Lys Ser Lys Ala Leu Ser Gly Phe Ser Leu Gln Ser
20 25 30

Cys Arg

(4) **INFORMATION FOR SEQ ID NO:3:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 5 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:3:

Pro Lys Glu Ser Gln
5

(5) INFORMATION FOR SEQ ID NO:4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single stranded

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:4:

Thr Ser Glu Ser Gly Leu
5

(6) INFORMATION FOR SEQ ID NO:5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 14 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single stranded

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:5:

Ser Thr Arg Ile Lys Lys Ser Lys Ala Leu Ser Gly Phe Ser
5 10

(7) INFORMATION FOR SEQ ID NO:6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 6 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS: single stranded

(D) TOPOLOGY: linear

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:6:

Thr Ser Glu Ser Gly Leu
5

(8) INFORMATION FOR SEQ ID NO:7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12 amino acids

(B) TYPE: amino acid

(C) STRANDEDNESS:

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:7:**

Thr Arg Ile Lys Lys Ser Lys Ala Leu Ser Gly Phe
5 10

(9) **INFORMATION FOR SEQ ID NO:8:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 6 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:8:**

Cys Ser Glu Ser Gly Cys
5

(10) **INFORMATION FOR SEQ ID NO:9:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 5 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:9:**

Cys Lys Glu Ser Cys
5

(11) **INFORMATION FOR SEQ ID NO:10:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 7 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:10:**

Cys Thr Arg Ile Lys Gly Cys
5

(12) **INFORMATION FOR SEQ ID NO:11:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 12 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:11:**

Cys Pro Glu Trp Pro Lys Glu Ser Gln Arg Pro Cys
5 10

(13) **INFORMATION FOR SEQ ID NO:12:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 8 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:12:**

Cys Gly Asp Ser Asp Ile Asp Cys
5

(14) **INFORMATION FOR SEQ ID NO:13:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 31 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:13:**

Phe Thr Cys Val Leu Lys Asp Ser Val Thr Glu Thr Leu Pro Arg
5 10 15

Val Asn Arg Thr Ala Ala Ile Ser Gly Tyr Ser Phe Lys Gln Cys
20 25 30

Ser

(15) **INFORMATION FOR SEQ ID NO:14:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 43 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:14:**

Ala Thr Arg Gln Phe Pro Ser Leu Glu His Arg Asn Ile Cys Leu
5 10 15

Leu Lys His Thr Gln Thr Gly Thr Pro Thr Arg Ile Thr Lys Leu
20 25 30

Asp Lys Val Val Ser Gly Phe Ser Leu Lys Ser Cys Ala
35 40

(16) **INFORMATION FOR SEQ ID NO:15:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 34 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:15:**

Ala Gln Ala Ser Cys Asn Glu Gly Lys Gly Lys Cys Tyr Leu Lys
5 10 15

Leu Ser Ser Asn Gly Ser pro Thr Lys Ile Leu His Gly Arg Gly
20 25 30

Gly Ile Ser Gly

(17) **INFORMATION FOR SEQ ID NO:16:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 6 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:16:**

His Ser Ile Pro Val Phe
5

(18) **INFORMATION FOR SEQ ID NO:17:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 12 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:17:**

Val Leu Lys Cys Ser Val Thr Glu Cys Leu Phe Arg
5 10

(19) **INFORMATION FOR SEQ ID NO:18:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 16 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:18:**

Phe Thr Cys Val Leu Lys Asp Ser Val Thr Glu Thr Leu Pro Arg
5 10 15

Val

(20) **INFORMATION FOR SEQ ID NO:19:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 15 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:19:**

Asn Arg Thr Ala Ala Ile Ser Gly Tyr Ser Phe Lys Gln Cys Ser
5 10 15

(21) **INFORMATION FOR SEQ ID NO:20:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 14 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:20:**

Cys Arg Thr Ala Ala Ile Ser Gly Tyr Ser Phe Lys Gln Cys
5 10

(22) **INFORMATION FOR SEQ ID NO:21:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 12 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:21:**

Asn Arg Thr Cys Ala Ile Ser Cys Tyr Ser Phe Lys
5 10

(23) **INFORMATION FOR SEQ ID NO:22:**

(i) **SEQUENCE CHARACTERISTICS:**

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:22:**

Thr Ala Glu Ser Pro Ser Glu Asp Pro Thr Arg Trp Phe Thr Cys
5 10 15

Val Leu Lys Asp Ser Val Thr Glu Thr Leu Pro Arg Val Asn Arg
20 25 30

Thr Ala Ala Ile Ser Gly Tyr Ser Phe Lys Gln Cys Ser
35 40

(24) **INFORMATION FOR SEQ ID NO:23:**

(i) **SEQUENCE CHARACTERISTICS:**

(A) **LENGTH:** 85 amino acids

(B) **TYPE:** amino acid

(C) **STRANDEDNESS:** single stranded

(D) **TOPOLOGY:** linear

(xi) **SEQUENCE DESCRIPTION: SEQ ID NO:23:**

## Claims

1. A synthetic peptide consisting essentially of an amino acid sequence from at least 5 to about 80 amino acids in length, which sequence corresponds to a portion of the sequence of the platelet binding site on the heavy chain of factor XI or factor XIa, said peptide having an artificially introduced restricted conformation and the ability to inhibit the binding of platelets to factor XI or factor XIa, or a pharmaceutically acceptable salt of said peptide, and wherein said artificially introduced restricted conformation is provided in part by at least one covalent bond other than a cysteine-cysteine disulfide bond when said peptide consists of an amino acid sequence according to SEQ ID NO:2.

2. A composition comprising a peptide attached to a linker sequence from about 1 to 100 amino acids in length, which may be further linked to a detectable label, solid matrix, or carrier, wherein said peptide is a peptide according to claim 1.

3. A peptide according to claim 1 wherein the peptide is from 5 to about 45 amino acids in length.

4. A peptide according to claim 3 wherein the peptide is from about 5 to about 20 amino acids in length.

5. A peptide according to claim 1 selected from the group of peptides having the following amino acid sequences corresponding to the amino acid sequence of the factor XI heavy chain:

amino acids 225-266;

amino acids 248-253.

6. A peptide according to claim 1 wherein the conformation is restricted by means of at least one cysteine-cysteine disulfide bond.

7. A peptide according to claim 1 which comprises a sequence according to SEQ ID No:7 and at least one cysteine-cysteine disulfide bond.

8. A peptide according to claim 1 wherein the restricted conformation is determined from the equilibrium conformation model comprising the set of coordinates and connect statement of Appendix 1.

9. A synthetic peptide consisting essentially of an amino acid sequence from at least 5 to about 80 amino acids in length, which sequence corresponds to a portion of the sequence of the platelet binding site on the heavy chain of factor XI or factor XIa, said peptide having an artificially introduced restricted conformation and the ability to inhibit the binding of platelets by factor XI or factor XIa, or a pharmaceutically acceptable salt of said peptide,

combinations thereof.

11. A peptide according to claim 10 having an amino acid sequence of D-Cys-(SEQ ID NO:7)-Cys.

12. A peptide according to claim 9 wherein the restricted conformation is determined from the equilibrium conformation model comprising the set of coordinates and connect statement of Appendix 1.

13. A synthetic peptide consisting essentially of an amino acid sequence from at least 5 to about 80 amino acids in length, which sequence corresponds to a portion of the sequence of the platelet binding site on the heavy chain of factor XI or factor XIa, said peptide having an artificially introduced restricted conformation and the ability to inhibit the binding of platelets by factor XI or factor XIa, or a pharmaceutically acceptable salt of said peptide,

wherein said restricted conformation is provided at least in part by at least one artificially introduced covalent bond other than a disulfide bond.

14. A peptide according to claim 13 wherein the conformation is restricted at least in part by at least one amide bond.

15. A peptide according to claim 13 wherein the conformation is restricted at least in part by at least one toluene-2,4-diisocyanate cross-link between two free amino groups of the peptide.

16. A peptide according to claim 14 wherein the conformation is restricted at least in part by at least one amide bond formed between side chains of a lysine residue and a glutamic or aspartic acid residue of the peptide.

17. A peptide according to claim 13 wherein the

amino acids 225-266;
amino acids 193-199;
amino acids 226-235;
amino acids 229-233;
amino acids 241-246;
amino acids 248-261; and
amino acids 248-253.

18. A peptide according to claim 13, wherein a segment of the sequence of said peptide consists of an amino acid sequence according to SEQ ID NO:7.

19. A peptide according to claim 13 wherein the restricted conformation is determined from the equilibrium conformation model comprising the set of coordinates and connect statement of Appendix 1.

20. A method of designing a peptide analog to the platelet binding site on the factor XI or factor XIa heavy chain comprising:

determining the distance between two parts of a molecular model including the platelet binding site at conformational equilibrium;

modifying the primary structure of the platelet binding site to restrict the distance between said two parts to the predetermined distance; and

synthesizing a peptide comprising said modified primary structure.

21. The method of claim 20 wherein the step of modifying the primary structure comprises introducing one or more cysteine residues to form an intramolecular disulfide bond.

22. The method of claim 20 wherein the step of

23. A method according to claim 20 wherein the the distance between said two parts is restricted to the predetermined distance by forming an amide bond linking two parts of the primary structure of the platelet binding site.

24. The method according to claim 22 wherein the step of modifying the primary structure comprises introducing an amino acid selected from the group consisting of lysine, glutamic acid and aspartic acid and reacting side chains of a lysine with a glutamic or aspartic acid residue to form an amide bond to restrict said two parts to the predetermined distance by internally cross-linking said primary structure.

25. The method according to claim 20 wherein the step of modifying the primary structure comprises introducing a toluene-2,4-diisocyanate structure to internally cross-link two free amino groups of the peptide.

26. The method according to claim 20 wherein the molecular model comprises the set of coordinates and connect statement of Appendix 1.

27. A method of producing a peptide having a restricted conformation comprising:

providing a peptide having an amino acid sequence corresponding to a portion of the sequence of the platelet binding site on the factor XI or factor XIa heavy chain;

determining the conformational equilibrium of that portion of the factor XI or factor XIa heavy chain; and

introducing a covalent modification into the peptide to restrict a distance between two parts of the peptide to a distance between two corresponding parts of the peptide in the equilibrium conformation determined.

28. The method of claim 27 wherein the modification comprises one or more cysteine residues capable

of forming an intramolecular cysteine-cysteine disulfide bond.

29. The method according to claim 27 wherein the modification comprises an amide bond cross-linking two parts of the peptide.

30. The method according to claim 29 wherein the modification comprises an amide bond cross-linking a lysine residue and a glutamic or aspartic acid residue.

31. The method according to claim 27 wherein the modification comprises a molecule of toluene-2,4-diisocyanate linking two amino groups.

32. The method according to claim 27 wherein the equilibrium conformation is determined according to the set of coordinates and connect statement of Appendix 1.

33. A pharmaceutical composition comprising one or more peptides of claim 1 and a pharmaceutically acceptable carrier.

34. A pharmaceutical composition comprising a peptide of claim 4 and a pharmaceutically acceptable carrier.

35. A pharmaceutical composition comprising one or more peptides of claim 8 and a pharmaceutically acceptable carrier.

36. A pharmaceutical composition according to claim 33 further comprising a second synthetic peptide having an amino acid sequence from at least 5 to about 50 amino acids in length wherein the amino acid sequence of said peptide corresponds to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, which peptide has an artificially restricted conformation and the ability to inhibit the binding of factor

XI to high molecular weight kininogen, or a pharmaceutically acceptable salt of said peptide.

37. A pharmaceutical composition according to claim 36 wherein the restricted conformation of said second peptide is determined from the equilibrium conformation model comprising the set of coordinates and connect statements of Appendix 2.

38. A pharmaceutical composition according to claim 36 wherein the restricted conformation of said second peptide is provided at least in part by at least one cysteine-cysteine disulfide bond, wherein at least one of the cysteine residues which form the disulfide bond is not present in the native amino acid sequence of the heavy weight kininogen binding site on the heavy chain of factor XI or factor XIa.

39. A pharmaceutical composition according to claim 36 wherein the restricted conformation of said second peptide is provided at least in part by at least by at least one artificially introduced covalent bond other than a disulfide bond.

40. A pharmaceutical composition according to claim 39 wherein the conformation of said second peptide is restricted at least in part by at least one amide bond.

41. A pharmaceutical composition according to claim 39 wherein the conformation of said second peptide is restricted at least in part by at least one toluene-2,4-diisocyanate cross-link between two free amino groups of said second peptide.

42. A pharmaceutical composition according to claim 40 wherein the conformation of said second peptide is restricted at least in part by at least one amide bond formed between side chains of a lysine residue and a glutamic or aspartic acid residue of the peptide.

43. A pharmaceutical composition according to claim 36 wherein said second peptide comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO:13;
SEQ ID NO:17;
SEQ ID NO:18;
SEQ ID NO:19;
SEQ ID NO:20;
SEQ ID NO:21; and
SEQ ID NO:22.

44. A method of inhibiting factor XIa-induced activation of factor IX on the surface of platelets comprising contacting platelets with one or more synthetic peptides comprising an amino acid sequence corresponding to a portion of the sequence of the platelet binding site on the heavy chain of factor XI, said peptide having a restricted conformation and the ability to inhibit the binding of platelets by factor XI or by factor XIa.

45. A method according to claim 44 wherein the conformation of said peptide is restricted at least in part by at least one a cysteine-cysteine disulfide bond, wherein at least one of the cysteine residues which form the disulfide bond is not present in the native amino acid sequence of the platelet binding site on the heavy chain of factor XI or factor XIa.

46. A method according to claim 44 wherein the restricted conformation of said peptide is provided at least in part by at least one artificially introduced covalent bond other than a cysteine-cysteine disulfide bond.

47. A method according to claim 44 wherein the restricted conformation of said the peptide is provided at least in part by at least one artificially introduced amide

48. A method according to claim 44 wherein the peptide is selected from the group of peptides having amino acid sequences selected from the group of sequences consisting of:

D-Cys-(SEQ ID NO:7)-Cys;
SEQ ID NO:8;
SEQ ID NO:9;
SEQ ID NO:10;
SEQ ID NO:11;
SEQ ID NO:12; and

combinations thereof.

49. A method according to claim 44 further comprising contacting platelets with a second synthetic peptide comprising an amino acid sequence from at least 5 to about 50 amino acids in length wherein the amino acid sequence of said second peptide corresponds to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, which second peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen, or a pharmaceutically acceptable salt of said second peptide.

50. A method according to claim 49 wherein the restricted conformation of said second peptide is determined from the equilibrium conformation model comprising the set of coordinates and connect statements of Appendix 2.

51. A method according to claim 49 wherein the restricted conformation of said second peptide is provided at lease in part by at least one artificially introduced covalent bond other than a disulfide bond.

52. A method according to claim 49 wherein the conformation of said second peptide is restricted at least in part by at least one amide bond.

53. A method according to claim 49 wherein the conformation of said second peptide is restricted at least

in part by at least one toluene-2,4-diisocyanate cross-link between two free amino groups of said second peptide.

54. A method according to claim 49 wherein the conformation of said second peptide is restricted at least in part by at least one amide bond formed between side chains of a lysine residue and a glutamic or aspartic acid residue of the peptide.

55. A method according to claim 49 wherein said second peptide comprises an amino acid sequence selected from the group consisting of:

SEQ ID NO:13;
SEQ ID NO:17;
SEQ ID NO:18;
SEQ ID NO:19;
SEQ ID NO:20;
SEQ ID NO:21; and
SEQ ID NO:22.

56. A method of inhibiting the binding of platelets to factor XI or factor XIa comprising contacting platelets with one or more synthetic peptides comprising an amino acid sequence corresponding to a portion of the sequence of the platelet binding site on the heavy chain of factor XI, said peptide having a restricted conformation and the ability to inhibit the binding of platelets to factor XI or to factor XIa.

57. A method according to claim 56 wherein the peptide is selected from the group of peptides having amino acid sequences selected from the group of sequences consisting of:

D-Cys-(SEQ ID NO:7)-Cys;
SEQ ID NO:8;
SEQ ID NO:9;

combinations thereof.

58. A method according to claim 56 further comprising contacting platelets with a second synthetic peptide comprising an amino acid sequence from at least 5 to about 50 amino acids in length wherein the amino acid sequence of said second peptide corresponds to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, which second peptide has an artificially restricted conformation and the ability to inhibit the binding of factor XI to high molecular weight kininogen, or a pharmaceutically acceptable salt of said second peptide.

59. A method for inhibiting thrombosis comprising administering to a mammal in need of such treatment an effective amount of one or more synthetic peptides comprising an amino acid sequence corresponding to a portion of the sequence of the platelet binding site on the heavy chain of factor XI, said peptide having a restricted conformation and the ability to inhibit the binding of platelets to factor XI or to factor XIa.

60. A method according to claim 59 wherein said synthetic peptide is a peptide according to claim 1.

61. A method according to claim 59 further comprising administering to a mammal in need of such treatment an effective amount of a second synthetic peptide comprising an amino acid sequence from at least 5 to about 50 amino acids in length wherein the amino acid sequence of said second peptide corresponds to a portion of the sequence of the binding site for high molecular weight kininogen on the heavy chain of XI, which second peptide has an artificially restricted conformation and the ability to inhibit the bind-

FIG. 1

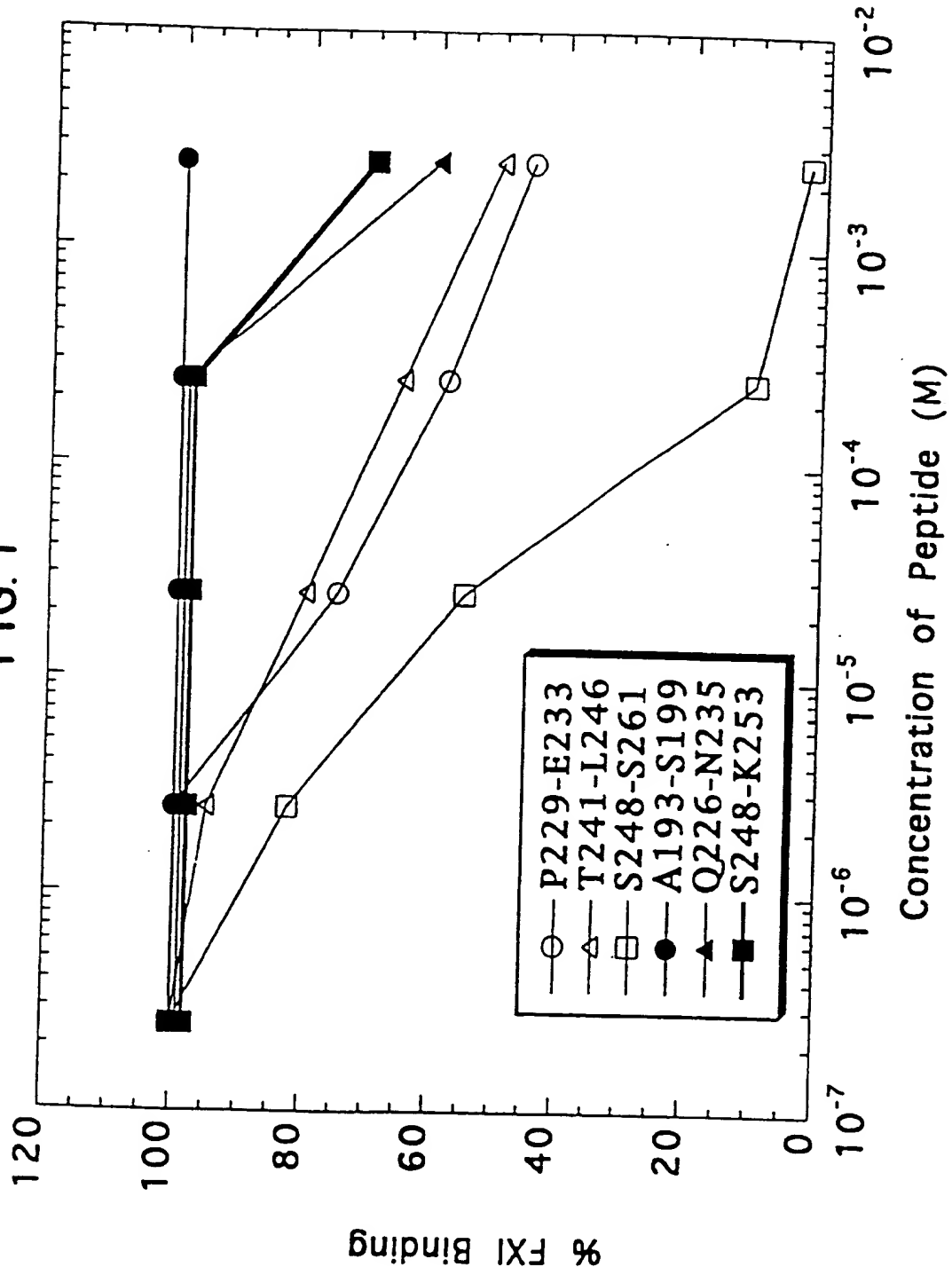
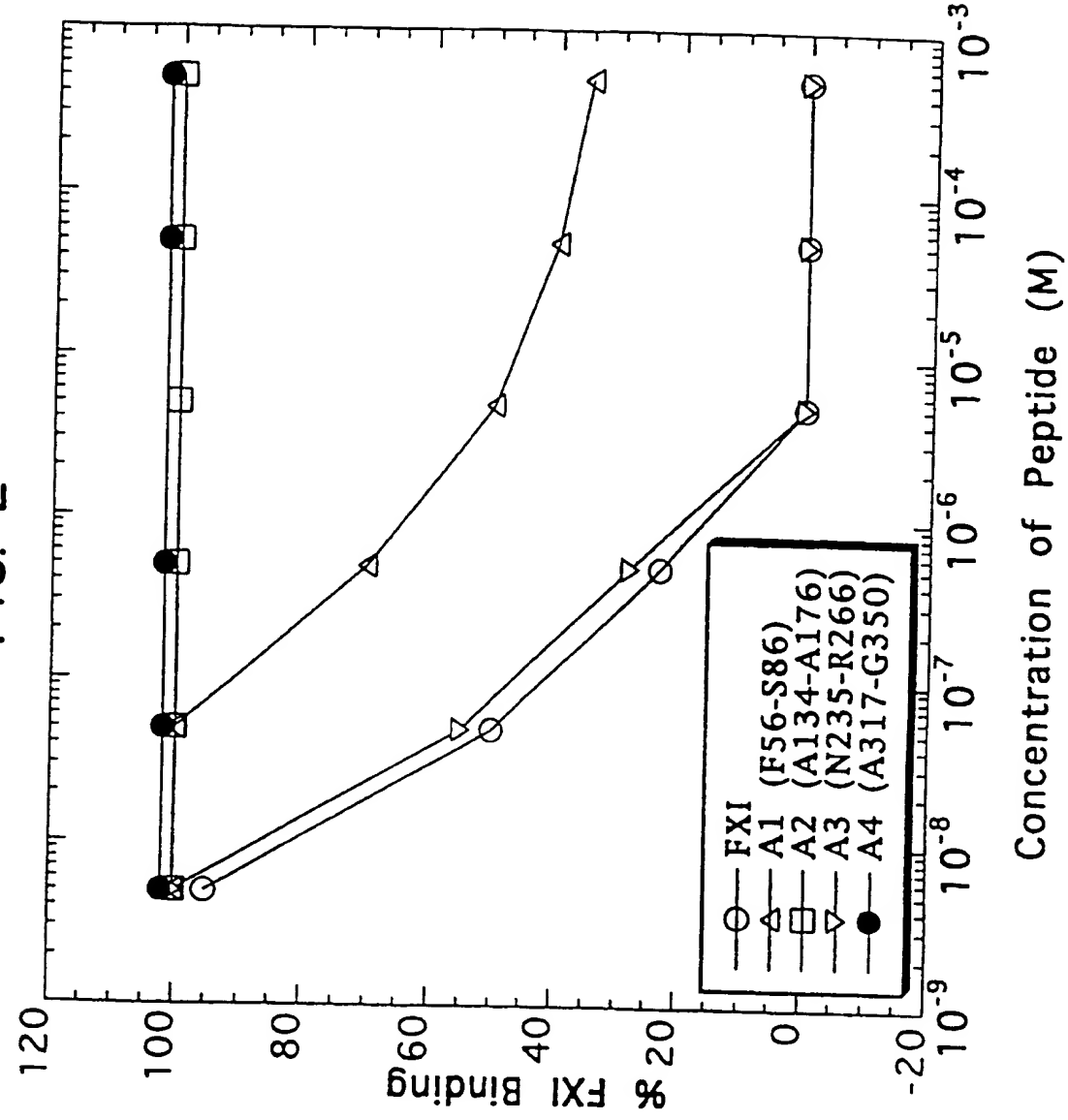

% FXI Binding
120
100
80
60
40
20
0
$10^{-7}$
$10^{-6}$
$10^{-5}$
$10^{-4}$
$10^{-3}$
$10^{-2}$
Concentration of Peptide (M)
P229-E233
T241-L246
S248-S261
A193-S199
Q226-N235
S248-K253

FIG. 2


% FXI Binding
120
100
80
60
40
20
0
-20
$10^{-9}$
$10^{-8}$
$10^{-7}$
$10^{-6}$
$10^{-5}$
$10^{-4}$
$10^{-3}$
Concentration of Peptide (M)
FXI
A1 (F56-S86)
A2 (A134-A176)
A3 (N235-R266)
A4 (A317-G350)

# INTERNATIONAL SEARCH REPORT

Ir ational application No.
PCT/US94/13885

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :C07K 7/00, 7/06, 7/08, 14/00; A61K 38/08, 38/10, 38/16

US CL :530/330, 329, 328, 327, 326, 325, 324; 514/12, 13, 14, 15, 16, 17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/330, 329, 328, 327, 326, 325, 324; 514/12, 13, 14, 15, 16, 17

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | Blood, Volume 79, No. 2, issued 15 January 1992, R. Rawala-Sheikh, "Role of γ-Carboxyglutamic Acid Residues in the Binding of Factor IXa to Platelets and in Factor-X Activation", pages 398-405, see entire document. | 1-61 |
| A | Biochemistry, Volume 25, issued 1986, A. D. Turner, "*p*-Amidino Esters as Irreversible Inhibitors of Factors IXa and Xa and Thrombin", pages 4929-4935, see entire document. | 1-61 |

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

| | | | |
|---|---|---|---|
| * | Special categories of cited documents: | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
| "A" | document defining the general state of the art which is not considered to be of particular relevance | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
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| "O" | document referring to an oral disclosure, use, exhibition or other means | | |
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| | |
|---|---|
| Date of the actual completion of the international search<br>20 MARCH 1995 | Date of mailing of the international search report<br>30 MAR 1995 |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703) 305-3230 | Authorized officer<br>CAROL A. SALATA<br>Telephone No. (703) 308-0196 |

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| A | The Journal of Biological Chemistry, Volume 267, No. 5, issued 15 February 1992, J. Astermark, "Effects of γ-Carboxyglutamic Acid and Epidermal Growth Factor-like Modules of Factor IX on Factor X Activation", pages 3249-3256, see entire document. | 1-61 |
| A | The Journal of Biological Chemistry, Volume 267, No. 12, issued 25 April 1992, S. S. Ahmad, "The Role of the First Growth Factor Domain of Human Factor IXa in Binding to Platelets and in Factor X Activation", pages 8571-8576, see entire document. | 1-61 |
| A | The Journal of Biological Chemistry, Volume 266, No. 35, issued 15 December 1991, F. A. Baglia, "Identification and Chemical Synthesis of a Substrate-binding Site for Factor IX on Coagulation Factor XIa", pages 24190-24197, see entire document. | 1-61 |